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(54) Title: NOVEL MAMMALIAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

(57) Abstract: Sequences and partial sequences for three types of mammalian (human and rat sequences identified) T-type calcium channel subunits which we have labeled as the α_{1G}, α_{1H} and α_{1I} subunits are provided. Knowledge of the sequence of these calcium channels permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel calcium channels of the invention. These cells may be used for identifying compounds capable of acting as agonists or antagonists to the calcium channels.

NOVEL MAMMALIAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

TECHNICAL FIELD

The invention relates to T-type calcium channel encoding sequences, expression of these sequences, and methods to screen for compounds which antagonize calcium channel activity. The invention is also related to molecular tools derived from knowledge of the molecular structure of T-type calcium channels.

BACKGROUND OF THE INVENTION

The rapid entry of calcium into cells is mediated by a class of proteins called voltage-gated calcium channels. Calcium channels are a heterogeneous class of molecules that respond to depolarization by opening a calcium-selective pore through the plasma membrane. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression. In neurons, calcium entry directly affects membrane potential and contributes to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Miller, R.J. (1987) "Multiple calcium channels and neuronal function." *Science* 235:46-52. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter. Calcium entry also plays a role in neurite outgrowth and growth cone migration in developing neurons and has been implicated in long-term changes in neuronal activity.

In addition to the variety of normal physiological functions mediated by calcium channels, they are also implicated in a number of human disorders. Recently, mutations identified in human and mouse calcium channel genes have been found to account for several disorders including, familial hemiplegic migraine, episodic ataxia type 2, cerebellar ataxia, absence epilepsy and seizures. Fletcher, *et al.* (1996) "Absence epilepsy in tottering mutant mice is associated with calcium channel defects." *Cell* 87:607-617; Burgess, *et al.* (1997) "Mutation of the Ca2+ channel

β subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse." *Cell* 88:385-392; Ophoff, *et al.* (1996) "Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4." *Cell* 87:543-552; Zhuchenko, O. *et al.* (1997) "Autosomal dominant cerebellar ataxia (SCA6) associated with the small polyglutamine expansions in the α_{1A}-voltage- dependent calcium channel." *Nature Genetics* 15:62-69.

The clinical treatment of some disorders has been aided by the development of therapeutic calcium channel antagonists. Janis, *et al.* (1991) in *Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance.* CRC Press, London.

Native calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey, *et al.* (1991) "Functional properties of voltage-dependent calcium channels." *Curr. Topics Membr.* 39: 295-326, and Dunlap, *et al.* (1995) "Exocytotic Ca^{2+} channels in mammalian central neurons." *Trends Neurosci.* 18:89-98.). T-type (or low voltage-activated) channels describe a broad class of molecules that activate at negative potentials and are highly sensitive to changes in resting potential. The L, N, P and Q-type channels activate at more positive potentials and display diverse kinetics and voltage-dependent properties. There is some overlap in biophysical properties of the high voltage-activated channels, consequently pharmacological profiles are useful to further distinguish them. L-type channels are sensitive to dihydropyridine (DHP) agonists and antagonists, N-type channels are blocked by the *Conus geographus* peptide toxin, ω-conotoxin GVIA, and P-type channels are blocked by the peptide ω-agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta.* A fourth type of high voltage-activated Ca channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather *et al.* (1993) "Distinctive biophysical and pharmacological properties of class A (B1) calcium channel α_1 subunits." *Neuron* 11:291-303; Stea, *et al.* (1994) "Localization and functional properties of a rat brain α_{1A} calcium channel reflect similarities to neuronal Q- and P-type channels." *Proc Natl Acad Sci (USA)* 91:10576-10580; Bourinet, E. *et al.* (1999) *Nature Neuroscience* 2:407-415). Several types of calcium conductances do not fall neatly into any of the above categories and there is variability of properties even within a category suggesting that additional calcium channels subtypes remain to be classified.

Biochemical analyses show that neuronal high-threshold calcium channels are heterooligomeric complexes consisting of three distinct subunits (α_1, $\alpha_2\delta$ and β) (reviewed by De Waard, *et al.* (1997) in *Ion Channels*, Volume 4, edited by Narahashi, T. Plenum Press, New York). The α_1 subunit is the major pore-forming subunit and contains the voltage sensor and binding sites for calcium channel antagonists. The mainly extracellular α_2 subunit is disulphide- linked to the transmembrane δ subunit and both are derived from the same gene and are proteolytically cleaved *in vivo*. The β subunit is a non-glycosylated, hydrophilic protein with a high affinity of binding to a cytoplasmic region of the α_1 subunit. A fourth subunit, γ is unique to L-type Ca channels expressed in skeletal muscle T-tubules. The isolation and characterization of γ-subunit-encoding cDNAs is described in U.S. Patent No. 5,386,025 which is incorporated herein by reference.

Molecular cloning has revealed the cDNA and corresponding amino acid sequences of six different types of α_1 subunits (α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E} and α_{1S}) and four types of β subunits (β_1, β_2, β_3 and β_4) (reviewed in Stea, A., Soong, T.W. and Snutch, T.P. (1994) "Voltage-gated calcium channels." in *Handbook of Receptors and Channels*. Edited by R.A. North, CRC Press). A comparison of the amino acid sequences of these α_1 subunits is included in this publication, which is incorporated herein by reference. PCT Patent Publication WO 95/04144, which is incorporated herein by reference, discloses the sequence and expression of α_{1E} calcium channel subunits.

As described in Stea, A. *et al.* (1994) (supra), the α_1 subunits are generally of the order of 2000 amino acids in length, ranging from 1873 amino acids in α_{1S} derived from rabbit to 2424 amino acids in α_{1A} derived from rabbit. Generally, these subunits contain 4 internal homologous repeats (I-IV) each having six putative alpha helical membrane spanning segments (S1-S6) with one segment (S4) having positively charged residues every 3rd or 4th amino acid. There are a minority of a splice variant exceptions. Between domains II and III there is a cytoplasmic domain which is believed to mediate excitation-contraction coupling in α_{1S} and which ranges from 100-400 amino acid residues among the subtypes. The domains I-IV make up roughly 2/3 of the molecule and the carboxy terminus adjacent to the S6 region of domain IV is believed to be on the intracellular side of the calcium channel. There is a consensus motif (QQ-E-L-GY-WI-E) in all of the subunits cloned and described in Stea, A. *et al.*

(supra) downstream from the domain I S6 transmembrane segment that is a binding site for the ß subunit.

PCT publication WO 98/38301, which describes the work of the inventors herein, and which is incorporated herein by reference, reports the first description of the molecular composition of T-type calcium channel α_1 subunits. The present application describes full-length genes for 3 mammalian subtypes, α_{1G}, α_{1H}, and α_{1I} associated with T-type calcium channels.

In some expression systems the high threshold α_1 subunits alone can form functional calcium channels although their electrophysiological and pharmacological properties can be differentially modulated by coexpression with any of the four β subunits. Until recently, the reported modulatory affects of β subunit coexpression were to mainly alter kinetic and voltage- dependent properties. More recently it has been shown that β subunits also play crucial roles in modulating channel activity by protein kinase A, protein kinase C and direct G-protein interaction. (Bourinet, *et al.* (1994) "Voltage-dependent facilitation of a neuronal α1C L-type calcium channel." *EMBO J.* 13: 5032-5039; Stea, *et al.* (1995) "Determinants of PKC- dependent modulation of a family of neuronal calcium channels." *Neuron* 15:929-940; Bourinet, *et al.* (1996) "Determinants of the G-protein-dependent opioid modulation of neuronal calcium channels." *Proc. Natl. Acad. Sci. (USA)* 93: 1486-1491.)

Because of the importance of calcium channels in cellular metabolism and human disease, it would be desirable to identify the remaining classes of α_1 subunits, and to develop expression systems for these subunits which would permit the study and characterization of these calcium channels, including the study of pharmacological modulators of calcium channel function.

DISCLOSURE OF THE INVENTION

The present invention provides sequences for a novel mammalian calcium channel subunits of T-type calcium channels, which we have labeled as α_{1G}, α_{1H} and α_{1I} subunits. Knowledge of the sequences of these calcium channel subunits may be used in the development of probes for mapping the distribution and expression of the subunits in target tissues. In addition, as the molecular structure of the α_1 subunits of these T-type calcium channels has been elucidated, it is possible to identify those

portions which reside extracellularly and thus to design peptides to elicit antibodies which can be employed to assess the location and level of expression of T-type calcium channels. In addition, these subunits, either alone or assembled with other proteins, can produce functional calcium channels, which can be evaluated in model cell lines to determine the properties of the channels containing the subunits of the invention. These cell lines can be used to evaluate the effects of pharmaceuticals and/or toxic substances on calcium channels incorporating α_{1G}, α_{1H} and α_{1I} subunits. The resulting identified compounds are useful in treating conditions where undesirable T-type calcium channel activity is present. These conditions include epilepsy, sleep disorders, mood disorders, cardiac hypertrophy and arrythmia and hypertension, among others. In addition, antisense and triplex nucleotide sequences can be designed to inhibit the production of T-type calcium channels.

In some embodiments of the methods and products of this invention, the α_1 subunits are other than those encoded by SEQ ID NO: 17; or, alternatively, are other than those encoded by SEQ ID NO: 17 and by the full length sequences of which SEQ ID NO: 19 and 21 are part. Other embodiments of the methods and products of this invention exclude probes representing portions of or all of SEQ ID NO: 13-21; or, alternatively, exclude probes representing portions of or all of SEQ ID NO: 1-22.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and B show a comparison of the waveforms and current voltage relationship for α_{1G};

Figs. 2A and B show a comparison of the waveforms and current voltage relationship for α_{1I} calcium channels.

Fig. 3 shows a comparison of the steady state inactivation profiles of the α_{1G} and α_{1I} calcium channels.

Figs. 4A-C show a comparison of the inactivation kinetics of the α_{1G} and α_{1I} calcium channels.

Figures 5A and 5B show the construction of the human α_{1G} cDNA complete sequence from partial clones.

Figure 6 shows the nucleotide and deduced amino acid sequence of human T-type calcium channel α_{1G}.

Figure 7 shows a comparison of the waveforms and current voltage relationship for human α_{1G} calcium channel.

Figure 8 shows the characteristic pore pattern for T-type channels.

MODES OF CARRYING OUT THE INVENTION

The present invention includes the following aspects for which protection is sought:

(a) novel mammalian (including human) calcium channel subunits and DNA sequences encoding such subunits. Specifically, the invention encompasses an at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α_1 subunit of a T-type calcium channel, and such α_1 subunits *per se*. It will be appreciated that polymorphic variations may be made or may exist in the DNA of some individuals leading to minor deviations in the DNA or amino acids sequences from those shown which do not lead to any substantial alteration in the function of the calcium channel. Such variations, including variations which lead to substitutions of amino acids having similar properties are considered to be within the scope of the present invention. Thus, in one embodiment, the present application claims DNA molecules which encode α_1 subunits of mammalian T-type calcium channels, and which hybridize under conditions of medium (or higher) hybridization stringency with one or another of the specific sequences disclosed in this application. This level of hybridization stringency is generally sufficient given the length of the sequences involved to permit recovery of the subunits within the scope of the invention from mammalian DNA libraries.

Alternatively, the T-type calcium channels of the invention are recognized by their functional characteristic of low voltage gating along with defined structural characteristics which classify them as α_1 calcium channel subunits and also characterize them as of the T-type. By virtue of the present invention, these characteristics have been elucidated as follows:

One distinguishing feature of the α_{1G}, α_{1H} and α_{1I} T-type channels over other types of calcium channels and sodium channels is that the pore region (P-region) in each of the four structural domains contains a diagnostic amino acid sequence implicated in channel permeability. Figure 8 shows that the T-type channels contain the residues glutamate/glutamate/aspartate/asparate (single letter amino acid code:

EEDD) in their P-regions (in domains I-IV). In contrast, figure 8 shows that in sodium (Na) channels the P-region of the four domains contains the residues: aspartate/glutamate/lysine/alanine (single letter amino acid code: DEKA), while high threshold calcium channels such as the L-type channel contain the residues: glutamate/glutamate/glutamate/glutamate (single letter amino acid code: EEEE). The α_{1G}, α_{1H} and α_{1I} T-type channels are also distinct in this region compared to other types of ion channels including the *C. elegans* C11D2.6 and C27F2.3 and the rat NIC-channel (Figure 8).

A second distinguishing characteristic of the α_{1G}, α_{1H} and α_{1I} T-type channels compared to other types of calcium channels is that they do not contain a β subunit binding consensus sequence in the cytoplasmic linker separating domains I and II. In contrast, all high threshold calcium channels contain a consensus sequence (single letter amino acid code: QQ-E--L-GY--WI---E) shown to physically interact with the calcium channel β subunit (Pragnell, M., De Waard, M., Mori, Y., Tanabe, T., Snutch, T.P. & Campbell, K.P., 1994, Nature 368:67-70). Thus, it appears the presence of a β subunit does not modify activity, nor is its presence required.

A third distinguishing characteristic of the (α_{1G}, α_{1H} and α_{1I} T-type channels is that they do not possess an EF-hand calcium binding motif in the region carboxyl to domain IV S6. In contrast, all high threshold calcium channels contain a consensus sequence that is closely related to the EF-hand domain found in certain calcium binding proteins (de Leon, M., Wang, Y., Jones, L., Perez-Reyes, E., Wei, X., Soong, T.W., Snutch, T.P. & Yue, D.T., 1995, Science270: 1502-1506).

Thus, as defined herein, "T-type calcium channel α_1 subunits" refers to subunits which contain these structural characteristics.

Alternatively, the T-type α_1 subunit molecules can be defined by homology to the human and rat nucleotide and amino acid sequences described herein. Thus, T-type α_1 subunits will typically have at least 50% and preferably 70% homology in terms of amino acid sequence or encoding nucleotide sequence to the sequences set forth in SEQ ID NOS. 23-28 herein or those shown in Figure 6. Preferably, the homology will be at least 80%, more preferably 90%, and most preferably 95%, 97%, 98% or 99%.

Relative homology may also be defined in terms of specific regions; as set forth above, certain regions of T-type channel α_1 subunits have very high homologies while other regions, such as the cytoplasmic region between domains II and III have less homology. Thus, T-type α_1 subunits will have over 75% homology, preferably over 85% or over 95% homology, more preferably over 98% homology in domains I-IV to those of SEQ ID NO: 23-28 or Figure 6. The degree of homology in the cytoplasmic region between domains II and III may be substantially less, *e.g.*, only 25% homology, preferably 50% homology or more preferably 60% homology. Similarly, the intracellular region downstream of domain IV may be less homologous than those within domains I-IV.

(b) polynucleotide sequences useful as probes in screening human cDNA libraries for genes encoding these novel calcium channel subunits. These probes can also be used in histological assay to determine the tissue distribution of the novel calcium channel subunits.

As set forth above, the elucidation herein of the structural features of T-type subunits permits the selection of appropriate probes by selecting portions of the encoding nucleotide sequence that are particularly characteristic of this type. As set forth above, for example, T-type subunits have particular patterns of amino acids in the pore forming units as set forth in Figure 8. Alternatively, multiple probes might be used to distinguish other subunits, such as probes which represent the β-binding domain missing from the T-type α_1 subunits combined with a probe representing a consensus sequence for calcium channel α subunits in general.

(c) at least partially purified α_1 subunits and related peptides for mammalian T-type calcium channels. These proteins and peptides can be used to generate polyclonal or monoclonal antibodies to determine the cellular and subcellular distribution of T-type calcium channel subunits.

Again, by virtue of the elucidation of the amino acid sequence of T-type α_1 subunits, it is well within the ordinary skill in the art to determine which regions of the channel are displayed extracellularly and to select these regions for the generation of antibodies.

(d) eukaryotic cell lines expressing the novel calcium channel subunits. These cell lines can be used to evaluate compounds as pharmacological modifiers of the function of the novel calcium channel subunits.

(e) a method for evaluating compounds as pharmacological modifiers of the function of the novel calcium channel subunits using the cell lines expressing those subunits alone or in combination with other calcium channel subunits.

(f) Use of the compounds identified as set forth above for the treatment of conditions which are associated with undesired calcium channel activity.

These diseases include, but are not limited to; epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression and Parkinson's disease; characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels.

T-type channels in particular are responsible for rebound burst firing in central neurons and are implicated in normal brain functions such as slow-wave sleep and in neurological disorders such as epilepsy and mood disorders. They are also important in pacemaker activity in the heart, hormone secretion and fertilization, and are associated with disease states such as cardiac hypertrophy and hypertension.

As used in the specification and claims of this application, the term "T-type calcium channel" refers to a voltage-gated calcium channel having a low activation voltage, generally less than -50 mV, and most commonly less than -60 mV. T-type calcium channels also exhibit comparatively negative steady-state inactivation properties and slow deactivation kinetics. The terms "α_1 subunit" or "α_1 calcium channel" refer to a protein subunit of a calcium channel which is responsible for pore formation and contains the voltage sensor and binding sites for calcium channel agonists and antagonists. Such subunits may be independently functional as calcium channels or may require the presence of other subunit types for complete functionality.

As used in the specification and claims of this application, the phrase "at least partially purified" refers to DNA or protein preparations in the which the specified molecule has been separated from adjacent cellular components and molecules with which it occurs in the natural state, either by virtue of performing a physical separation process or by virtue of making the DNA or protein molecule in a non-natural environment in the first place. The term encompasses cDNA molecules and expression vectors.

In accordance with the present invention, we have identified mammalian DNA sequences which code for novel T-type calcium channel α_1 subunits. These subunits are believed to represent new types of α_1 subunits of mammalian voltage-dependent calcium channels which have been designated as types α_{1G}, α_{1H} and α_{1I}.

A Bacterial Artificial Chromosome (BAC) sequence (bK206c7) was identified from sequences in Sanger Genome Sequencing Center (Cambridge, U.K.) and the Washington University Genome Sequencing Center (St. Louis. MO) that contains a nucleotide sequence encoding the α_{1I} subunit of human T-type calcium channel. The rationale for this identification is set forth in WO 98/38301, incorporated herein by reference. The relevant nucleotide sequence and the translated amino acid sequence containing 1854 amino acids are set forth in SEQ ID NO:17 and 18.

As described in WO 98/38031, using PCR cloning techniques to identify relevant sequences within a human brain total RNA preparation, we confirmed that the novel α_{1I} calcium channel subunit is present in human brain. Subcloning of the 567 nt PCR product (Seq. ID No. 19, amino acids Seq. ID No. 20) and subsequent sequencing thereof showed that this product corresponds to the derived sequence from the bK206c7 BAC genomic sequence, the nucleotide sequence of which is given as SEQ ID No. 17 (amino acid sequence Seq. ID No. 18). The same experiment was performed using a rat brain RNA preparation and resulted in recovery of a substantially identical PCR product. (SEQ ID. No. 21). The protein encoded by the rat PCR product (SEQ ID No. 22) is 96% identical to the human PCR product (Seq. ID No. 20).

These sequences, which encode a partial subunit were used as a basis for constructing full length human or rat α_{1I} clones. Briefly, the subcloned α_{1I} PCR product is radiolabeled by random hexamer priming according to standard methods (See, Sambrook , J., Fritsch, E.F. and Maniatis, T. (1989) *Molecular Cloning, A Laboratory Manual*. Cold Spring Harbor Press) and used to screen commercial human brain cDNA libraries (Stratagene, La Jolla, CA). The screening of cDNA libraries follows standard methods and includes such protocols as infecting bacteria with recombinant lambda phage, immobilizing lambda DNA to nitrocellulose filters and screening under medium hybridization stringency conditions with radiolabeled probe. cDNA clones homologous to the probe are identified by autoradiography. Positive clones are purified by sequential rounds of screening.

Following this protocol, most purified cDNA's are likely to be partial sequence clones due the nature of the cDNA library synthesis. Full length clones are constructed from cDNA's which overlap in DNA sequence. Restriction enzyme sites which overlap between cDNAs are used to ligate the individual cDNA's to generate a full-length cDNA. For subsequent heterologous expression, the full-length cDNA is subcloned directly into an appropriate vertebrate expression vector, such as pcDNA-3 (Invitrogen, San Diego, CA) in which expression of the cDNA is under the control of a promoter such as the CMV major intermediate early promoter/enhancer. Other suitable expression vectors include, for example, pMT2, pRC/CMV, pcDNA3.1 and pCEP4.

Following these protocols, full length mammalian α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs were isolated by using the 567 base pair human fragment (Seq. ID No. 19) to screen a rat brain cDNA library. Sequencing of the recovered sequences identified the three distinct classes of calcium channel subunits which have been denominated herein as α_{1G}, α_{1H} and α_{1I} subunits. For each class of subunit, complete sequencing of the largest cDNA confirmed that it represented only a portion of the predicted calcium channel coding region. Complete sequences for the three new subunits were obtained by rescreening the rat brain cDNA library with probes derived from the partial length cDNAs to obtain overlapping segments. These segments were combined to form a complete gene by restriction digestion and ligation. The complete cDNA sequences of the rat α_{1G}, α_{1H} and α_{1I} subunits are given by Sequence ID Nos. 23, 25 and 27, respectively. Corresponding amino acid sequences are given by Sequence ID Nos. 24, 26 and 28. The same techniques are employed to recover human sequences by screening of a human or other mammalian library. Thus, for example, partial length human sequences for α_{1G} and α_{1H} T- type calcium channels have been recovered using the same probe (Seq. ID No. 19) and the full length rat α_{1I} cDNA (Seq. ID. No. 27) has been used to recover a partial length DNA encoding a human α_{1I} T-type calcium channel. The DNA and amino acid sequences for these partial length human calcium channels are given by Seq. ID Nos. 30-35. A complete coding sequence for human α_{1G} was obtained and is set forth, along with the deduced amino acid sequence, in Figure 6.

Once the full length cDNA is cloned into an expression vector, the vector is then transfected into a host cell for expression. Suitable host cells include *Xenopus*

oocytes or mammalian cells such as human embryonic kidney cells as described in International Patent Publication No. WO 96/39512 which is incorporated herein by reference and Ltk cells as described in US Patent No. 5,386,025 which is incorporated herein by reference. Transfection into host cells may be accomplished by microinjection, lipofection, glycerol shock, electroporation calcium phosphate or particle-mediated gene transfer. The vector may also be transfected into host cells to provide coexpression of the novel α_1 subunits with other subunits, such as an $\alpha_2\delta$ subunit or a γ subunit.

To confirm that the three full length cDNAs (sequence ID Nos. 23, 25 and 27) encoded functional calcium channels, the α_{1G} and α_{1I} cDNAs were transiently transfected into human embryonic kidney cells and evaluated using electrophysiological recording techniques. The results are consistent with a role of these subunits in native T-type channels in nerve, muscle and endocrine cells. Similarly, a full length clone encoding human α_{1G} T-type subunit was recovered and verified to have the characteristic properties of T-type channels.

The resulting cell lines expressing functional calcium channels including the novel α_1 subunits of the invention can be used test compounds for pharmacological activity with respect to these calcium channels. Thus, the cell lines are useful for screening compounds for pharmaceutical utility. Such screening can be carried out using several available methods for evaluation of the interaction, if any, between the test compound and the calcium channel. One such method involves the binding of radiolabeled agents that interact with the calcium channel and subsequent analysis of equilibrium binding measurements including but not limited to, on rates, off rates, K_d values and competitive binding by other molecules. Another such method involves the screening for the effects of compounds by electrophysiological assay whereby individual cells are impaled with a microelectrode and currents through the calcium channel are recorded before and after application of the compound of interest. Another method, high-throughput spectrophotometric assay, utilizes the loading the cell lines with a fluorescent dye sensitive to intracellular calcium concentration and subsequent examination of the effects of compounds on the ability of depolarization by potassium chloride or other means to alter intracellular calcium levels. Compounds to be tested as agonists or antagonists of the novel α_{1I} calcium channel subunits are combined with cells that are stably or transiently transformed with a

DNA sequence encoding the α_{1G}, α_{1H} and α_{1I} calcium channel subunits of the invention and monitored using one of these techniques.

Compounds which are shown to modulate the activity of calcium channels can then be used in pharmaceutical compositions for the treatment associated with inappropriate T-type calcium channel activity. Such conditions may also include those with inappropriate calcium channel activity in general since such activity may be modified by enhancing or decreasing T-type channel activity. Conditions appropriate for such treatment include those set forth above. The compounds identified are formulated in conventional ways as set forth in Remington's "Pharmaceutical Sciences," latest edition, Mac Publishing Co., Easton, PA. Modes of administration are those appropriate for the condition to be treated and are within the ordinary skill of the practitioner.

In addition, the regulation of expression of T-type calcium channels can be achieved by constructing expression systems encoding antisense sequences or sequences designed for triplex binding to interrupt the expression of nucleotide sequences encoding the T-type calcium channels of the invention.

DNA fragments with sequences given by SEQ ID Nos. 13-17 and 19, or polynucleotides with the complete coding sequences as given by Sequence ID Nos. 23, 25 and 27 or Figure 6, or distinctive portions thereof which do not exhibit non-discriminatory levels of homology with other types of calcium channel subunits may also be used for mapping the distribution of α_{1G}, α_{1H} and α_{1I} calcium channel subunits within a tissue sample. This method follows normal histological procedures using a nucleic acid probe, and generally involves the steps of exposing the tissue to a reagent comprising a directly or indirectly detectable label coupled to a selected DNA fragment, and detecting reagent that has bound to the tissue. Suitable labels include fluorescent labels, enzyme labels, chromophores and radio-labels.

Heterologous Expression of Mammalian T-type Calcium Channels in Cells

A. Transient Transfection in Mammalian Cells

Host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) are grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells are transfected by a standard calcium-phosphate-DNA co-precipitation method using a full-length mammalian α_1 T-type

calcium channel cDNA (for example, Seq. ID. No. 27) in a vertebrate expression vector (for example see Current protocols in Molecular Biology). The α_{1I} calcium channel cDNA may be transfected alone or in combination with other cloned subunits for mammalian calcium channels, such as $\alpha 2\delta$ and β or γ subunits, and also with clones for marker proteins such the jellyfish green fluorescent protein.

Electrophysiological Recording: After an incubation period of from 24 to 72 hrs the culture medium is removed and replaced with external recording solution (see below). Whole cell patch clamp experiments are performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to an IBM compatible personal computer equipped with pCLAMP software. Microelectrodes are filled with 3 M CsCl and have typical resistances from 0.5 to 2.5 M ohms. The external recording solution is 2 mM $BaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEACl, 10 mM Glucose, 92 mM CsCl, (pH 7.2). The internal pipette solution is 105 mM CsCl, 25 mM TEACl, 1 mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES (pH 7.2). Currents are typically elicited from a holding potential of -100 mV to various test potentials. Data are filtered at 1 kHz and recorded directly on the harddrive of a personal computer. Leak subtraction is carried out on-line using a standard P/5 protocol. Currents are analyzed using pCLAMP versions 5.5 and 6.0. Macroscopic current-voltage relations are fitted with the equation $I = \S 1/(1+\exp(-(V_m-V_h)/S)\} \times G - (V_m-E_{rev})$, where V_m is the test potential, V_h is the voltage at which half of the channels are activated, and S reflects the steepness of the activation curve and is an indication of the effective gating charge movement. Inactivation curves are normalized to 1 and fitted with $I = (1/1 + \exp((V_m-V_h)/S)$ with V_m being the holding potential. Single channel recordings are performed in the cell-attached mode with the following pipette solution (in mM): 100 $BaCl_2$, 10 HEPES, pH 7.4 and bath solution: 100 KCl, 10 EGTA, 2 $MgCl_2$, 10 HEPES, pH 7.4.

B. Transient Transfection in Xenopus Oocytes

Stage V and VI Xenopus oocytes are prepared as described by Dascal et al (1986), Expression and modulation of voltage-gated calcium channels after RNA injection into Xenopus oocytes. Science 231:1147-1150. After enzymatic dissociation with

collagenase, oocytes nuclei are microinjected with the human a_{1I} calcium channel cDNA expression vector construct (approximately 10 ng DNA per nucleus) using a Drummond nanoject apparatus. The α_{1I} calcium channel may be injected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b and γ subunits. After incubation from 48 to 96 hrs macroscopic currents are recorded using a standard two microelectrode voltage-clamp (Axoclamp 2A, Axon Instruments, Burlingame, CA) in a bathing medium containing (in mM): 40 Ba(OH)2,, 25 TEA-OH, 25 NaOH, 2 CsOH, 5 HEPES (pH titrated to 7.3 with methan-sulfonic acid). Pipettes of typical resistance ranging from 0.5 to 1.5 M ohms are filled with 2.8M CsCl, 0.2M CsOH, 10mM HEPES, 10mM BAPTA free acid. Endogenous Ca (and Ba) -activated Cl currents are suppressed by systematically injecting 10-30 nl of a solution containing 100mM BAPTA-free acid, 10mM HEPES (pH titrated to 7.2 with CsOH) using a third pipette connected to a pneumatic injector. Leak currents and capacitive transients are subtracted using a standard P/5 procedure.

Construction of Stable Cell Lines Expressing Mammalian T-type Calcium Channels

Mammalian cell lines stably expressing human α_{1I} calcium channels are constructed by transfecting the α_{1I} calcium channel cDNA into mammalian cells such as HEK 293 and selecting for antibiotic resistance encoded for by an expression vector. Briefly, a full-length mammalian T-type calcium channel α_1 subunit cDNA (for example Seq. ID No. 27) subcloned into a vertebrate expression vector with a selectable marker, such as the pcDNA3 (InvitroGen, San Diego, CA), is transfected into HEK 293 cells by calcium phosphate coprecipitation or lipofection or electroporation or other method according to well known procedures (Methods in Enzymology, Volume 185, Gene Expression Technology (1990) Edited by Goeddel, D.V.). The α_{1I} calcium channel may be transfected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b subunits, either in a similar expression vector or other type of vector using different selectable markers. After incubation for 2 days in nonselective conditions, the medium is supplemented with Geneticin (G418) at a concentration of between 600 to 800 ug/ml. After 3 to 4 weeks in this medium, cells which are resistant to G418 are visible and can be cloned as isolated colonies using standard cloning rings. After growing up

each isolated colony to confluency to establish cell lines, the expression of α_{1I} calcium channels can be determined at with standard gene expression methods such as Northern blotting, RNase protection and reverse-transcriptase PCR.

The functional detection of α_{1I} calcium channels in stably transfected cells can be examined electrophysiologically, such as by whole patch clamp or single channel analysis (see above). Other means of detecting functional calcium channels include the use of radiolabeled ^{45}Ca uptake, fluorescence spectroscopy using calcium sensitive dyes such as FURA-2, and the binding or displacement of radiolabeled ligands that interact with the calcium channel.

EXAMPLE 1

Partial Rat and Human Subunits

In order to recover mammalian sequences for novel calcium channels, the 567 base pair partial length human brain α_{1I} cDNA described in WO 98/3801 was gel-purified, radio-labelled with ^{32}P dATP and dCTP by random priming (Feinberg et al., 1983, *Anal. Biochem.* 132: 6-13) and used to screen a rat brain cDNA library constructed in the phase vector Lambda Zapp II. (Snutch *et al.*, 1990, *Proc Natl Acad Sci (USA)* 87: 3391-3395). Screening was carried out at 62°C in 5XSSPE (1XSSPE= 0.18 M NaCl; 1mM EDTA; 10 mM sodium phosphate, pH=7.4 0.3% SDS, 0.2 mg/ml denatured salmon sperm DNA). Filters were washed at 62°C in 0.2X SSPE/0.1% SDS. After three rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, La Jolla, CA) by *in vivo* excision.

Double stranded DNA sequencing on the recombinant phagemids was performed using a modified dideoxynucleotide protocol (Biggin *et al.*, 1983, *Proc Natl Acad Sci (USA)* 80:3963-3965) and Sequenase version 2.1 (United States Biochemical Corp.). DNA sequencing identified three distinct classes of calcium channel α_1 subunits: designated as α_{1G}, α_{1H} and α_{1I} calcium channel subunits.

For each class of calcium channel α_1 subunit, the largest cDNA was completely sequenced and determined to represent only a portion of the predicted calcium channel coding region. In order to isolate the remaining portions of α_{1G} and α_{1I} calcium channel subunits, the α_{1G} clone was digested with HindIII and SpeI. The resulting 540 base pair fragment was gel purified, radiolabeled with ^{32}P dATP and dCTP by random priming and used to rescreen the rat brain cDNA library as described above. The sequence of the 540 base pair α_{1G} screening probe used is given

by Seq. ID No. 29. Other sequences spanning regions of distinctiveness within the sequences for the subunits could also be employed.

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions.

To recover further human sequences for the novel α_{1G} and α_{1H} calcium channels, the 567 base pair partial length human brain α_{1I} cDNA (Seq. 19) was radio-labelled with ^{32}P dATP and dCTP by random priming and used to screen a commercial human thalamus cDNA library (Clontech). Hybridization was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were selected, DNA prepared and the insert cDNA excised from the lambda vector by digestion with Eco R1 restriction enzyme. The excised cDNA was subcloned into the plasmid Bluescript KS (Stratagene, La Jolla, CA) and the DNA sequence determined using a modified dideoxynucleotide protocol and Sequence version 2.1. The partial length α_{1G} cDNA isolated consisted of 2212 base pairs of which 279 base pairs were 5' noncoding and 1,933 base pairs were coding region representing 644 amino acids (Seq. ID Nos. 30, 31). The partial α_{1H} cDNA isolated consisted of 1,608 base pairs of which 53 base pairs were 5' noncoding and 1,555 were coding region representing 518 amino acids (Seq. ID Nos. 32, 33).

To recover further human sequences for the novel α_{1I} calcium channel, the full-length rat brain α_{1I} cDNA (Seq. 27; see example 2) was radio-labelled ^{32}P dATP and dCTP by random priming and used to screen a commercial human hippocampus cDNA library (Stratagene). Hybridization was performed overnight at 65°C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65° C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, LA Jolla, CA) by *in vitro* excision. The excised cDNA DNA sequence was determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial α_{1I} cDNA isolated

consisted of 1,080 base pairs of coding region representing 360 amino acids (Seq. ID Nos. 34, 35).

EXAMPLE 2

Full Length Rat Subunits

Double-stranded DNA sequencing of the purified recombinant phagemids from rat brain showed that additional α_{1G} and α_{1I} calcium channel cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions. (Seq. ID Nos. 23 and 27, respectively) In addition to the α_{1G} and α_{1I} calcium channel classes, DNA sequencing of the recombinant phagemids also identified a third class of calcium channel α_1 subunit: designated as the α_{1H} calcium channel subunit. The partial length α_{1H} calcium channel cDNAs overlapped and together encoded a complete α_{1H} coding region as well as portions of the 5' and 3' untranslated regions (Seq. ID. No. 25).

Electrophysiological studies were performed on transiently-transfected human embryonic kidney cells (HEK-tsa201) prepared using the general protocol above. Transfection was carried out by standard calcium phosphate precipitation. (Okayama *et al.*, 1991, *Methods in Molec. Biol.*, Vol. 7, ed. Murray, E.J.). For maintenance, HEK-tsa201 cells were cultured until approximately 70% confluent, the media removed and cells dispersed with trypsin and gentle trituration. Cells were then diluted 1:10 in culture medium (10% FBS, DMEM plus L-glutamine, pen-strp) warmed to 37°C and plated onto tissue culture dishes. For transient transfection, 0.5 mM $CaCl_2$ was mixed with a total of 20 µg of DNA (consisting of 3µg of either rat brain α_{1G} or α_{1I} calcium channel cDNA, 2 µg of CD8 plasmid marker, and 15 µg of Bluescript plasmid carrier DNA). The DNA mixture was mixed thoroughly and then slowly added dropwise to 0.5 ml of 2 times HeBS (274 mM NaCl, 20mM D-glucose, 10mM KCl, 1.4 mM Na_2HPO_4, 40 mM Hepes (pH=7.05). After incubation at room temperature for 20 min, 100 µl of the DNA mixture was slowly added to each dish of HEK-tsa201 cells and then incubated at 37°C for 24 to 48 hours in a tissue culture incubator (5% CO_2).

Positive transfectant cells were identified visually by addition of 1 µl of mouse CD8 (Lyt2) Dynabeads directly to the recording solution and gentle swirling to mix. Whole cell patch clamp readings were carried out with an Axopatch 200A amplifier

(Axon Instruments) as described previously. (Zamponi *et al.*, 1997, *Nature* 385: 442-446). The external recording solution was 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEA-Cl, 10 mM glucose, 92 mM CsCl, pH=7.2 with TEA-hydroxide. The internal pipette solutions was 105 mM CsCl, 25 mM TEA-Cl, 1mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES, pH 7.2 with NaOH.

For determination of current-voltage (I-V) relationships, cells were held at a resting potential of -100 mV and then stepped to various depolarizing test potentials. For steady-state inactivation, cells were held at varius potentials for 20 sec. and currents recorded during a subsequent test pulse to the peak potential of the I-V. Leak currents and capacitative transients were subtracted using a P/5 procedure.

Figs. 1-4 show the results obtained for HEK cells transfected with and expressing the cDNA of sequences ID Nos. 23 and 27, which correspond to the subunits designated as α_{1G} and α_{1I}. Figs. 1A and B and 2A and B shows a comparison of the waveforms and current- voltage relationship for the two channel subunit types. In the presence of recording solution containing 2mM Ca^{2+}, both the α_{1G} and α_{1I} channel subunits exhibit activation properties consistent with native T-type calcium currents. Figs 1 A and 2A show the subunit calcium current from a cell held at -120 mV and depolarized to a series of test potentials. Figs 1B and 2B show the magnitude of the calcium current. From a holding potential of -110 mV, both channel first activate at approximately -70 mV and peak currents are obtained between -40 and -50 mV. Upon depolarization to various test potentials, the current waveforms of the α_{1G} and α_{1I} calcium channels exhibit an overlapping pattern characteristic of native T-type channels in nerve, muscle and endocrine cells.

Fig. 3 shows steady-state inactivation profiles for the α_{1G} and α_{1I} calcium channels in HEK 293 cells transiently transformed with full length cDNAs (SEQ ID Nos 23 or 27) for α_{1G} or α_{1I} subunits. Steady state inactivation properties were determined by stepping from -120 mV to prepulse holding potentials between -120 mV and -50 mV for 15 sec.. prior to a test potential of -30 mV. The data are plotted as normalized whole cell current versus prepulse holding potential and show that α_{1G} exhibits a V_{50} of approximately -85 mV and α_{1I} a V_{50} of approximately -93 mV. Thus, consistent with native T-type calcium channels, both of the α_{1G} and α_{1I} calcium channels exhibit pronounced steady-state inactivation at negative potentials.

Figs. 4A-C show a comparison of the voltage-dependent deactivation profiles of the α_{1G} and α_{1I} calcium channels. HEK 293 cells were transiently transfected with either an α_{1G} or α_{1I} subunit cDNA (Seq. ID No. 23 or 27). The deactivation properties of α_{1G} were determined by stepping from a holding potential of -100 mV to -40mV for 9 msec, and then to potentials between -120 mV and -45 mV. The deactivation properties of α_{1I} were determined by stepping from a holding potential of -100 mV to -40 mV for 20 msec, and then to potentials between -120 mV and -45 mV. Both channels exhibit slow deactivation kinetics compared to typical high-threshold channels, and is consistent with the α_{1G} and α_{1I} subunits being subunits for T-type calcium channels

Example 3

Cloning of a Full Length cDNA for the Human $\alpha 1_G$ T-Type Calcium Channel Subunit

Materials and Methods:

A full length cDNA encoding the human α_{1G} subunit was constructed from 5 overlapping clones (Figure 1B) isolated from a human thalamus cDNA library constructed in λgt11 vector (Clontech, Cat#HL5009b).

Three λgt11 cDNA clones were isolated by conventional filter hybridization. Clone 1 was identified by hybridization to a 567 bp cDNA probe (SEQ ID NO: 19) containing the transmembrane region S4 to S6 of domain I of the previously cloned human neuronal α_{1I} T-type calcium channel subunit. Clones HG10-1112 and HG5-1211 were identified by hybridization to a 1265 bp cDNA probe of the rat α_{1H} T-type calcium channel subunit spanning domain II and part of the II-III intracellular loop. cDNA probes were ^{32}P-dCTP labelled by random priming using a Multiprime DNA labeling system (Amersham Pharmacia). Plaque lifts using H-bond nylon membranes were done in duplicate following the standard protocols supplied by manufacturer (Amersham Pharmacia). Hybridization was performed for at least 16hrs at 65°C for clone 1 and for at least 16hrs at 58° C, clones HG10-1112 and HG5-1211. Membranes were washed in 0.1X SSC/0.3% SDS at 62°C for clone 1 and 0.2X SSC/0.1% SDS at 58°C clones HG10-1112 and HG5-1211. Blots were exposed to BioMax MS Kodak film with Kodak HE intensifying screens for at least 48hrs at –80°C. Double positive plaques were isolated and re-screened to isolate single clones

according to the procedure above. Bacteriophage DNAs were then isolated according to the λgt11 library User Manual (Clontech). Clone 1 cDNA insert was excised with EcoRI (NEB) and subcloned into pBluescriptKS (Stratagene). Clones HG10-1112 and HG5-1211 cDNA inserts were excised from λDNA with Not I (NEB) and subcloned into the Not I site of pBluescriptKS. Plasmids with cDNA inserts were transformed by electroporation into XL-I E.Coli host strain bacteria and sequenced using universal reverse and forward primers according to Sanger double stranded DNA sequencing method in combination with automatic sequencing ABI 100 PRISM model 377 Version3.3 (PE Biosystems).

Clone 1 was identified as a human α_{1G} subunit containing the 5'UTR and 1933 bp of the in-frame coding region, including part of the intracellular I-II loop. Clone HG10-1112 was identified as a human α_{1G} subunit of 3915 bp, spanning Domain I (IS5-IS6) to the III-IV loop. Clone HG5-1211 was identified as human α_{1G} subunit of 3984 bp containing the I-II linker and C-terminus.

For expression in HEK cells, removal of 5' UTR from clone 1 was achieved by replacing 5'UTR DNA fragment flanked by Hind III/SacII restriction sites with 5'end - 291 bp cDNA fragment, containing translation start site and an incorporated Hind III site for subsequent cloning into pcDNA3.1 (Invitrogen). Following PCR conditions were used: 94°C –30 sec, 45°C –30 sec, 72°C –30 sec for 5 cycles and followed by 94°C –30 sec, 48°C –30 sec, 72°C –30 sec for 20 cycles (Bio-rad Gene Cycler). The cDNA fragment was subcloned into p-Gem-T-Easy plasmid vector (Promega) and the DNA sequence determined.

The remaining region of the 3' α_{1G} subunit cDNA was obtained using the PCR method on a human thalamus cDNA library with primers MD19-sense (5'GCG TGG AGC TCT TTG GAG 3') and G26- antisense (5' GCA CCC AGT GGA GAA AGG TG 3'). The PCR protocol used was 94°C –30 sec, 58°C –30 sec, 72°C –30 sec for 25 cycles (Bio-rad Gene Cycler). A cDNA fragment of 1617 bp was subcloned into p-Gem-T-Easy plasmid vector (Promega) and sequenced. The 3'PCR cDNA was identified as a human α_{1G} subunit spanning from Domain IV-S5 to the carboxyl terminus including the stop codon.

Unique restriction sites (Figures 5A and B) of the partial cDNA clones were used to construct the full length human α_{1G} T-type calcium channel in pcDNA3.1 Zeo

(+) (Invitrogen) mammalian expression vector.

The complete nucleotide and amino acid sequences are shown in Figure 6.

In order to determine the functional properties of the human α_{1G} channel standard calcium-phosphate transfection was used to transiently express the channel in HEK ts201 cells. Cells were cultured in Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum, 200 U/ml penicillin and 0.2 mg/ml streptomycin at 37°C with 5% CO_2. At 85% confluency cells were split with 0.25% trypsin/1 mM EDTA and plated at 10% confluency on glass coverslips. At 12 hours the medium was replaced and the cells transiently transfected using a standard calcium phosphate protocol and the α_{1G} calcium channel cDNA. Fresh DMEM was supplied and the cells transferred to 28°C/5% CO_2. Cells were incubated for 1 to 2 days prior to whole cell recording. Whole cell patch recordings were performed using an Axopatch 200B amplifier (Axon Instruments) linked to an IBM compatible personal computer equipped with pCLAMP version 7.0 software. The intrapipette solution contained (in mM): 105 CsCl, 25 CsCl, 1 $CaCl_2$, 11 EGTA, 10 HEPES, pH 7.2. The extracellular solution contained (in mM): 40 TEA-Cl, 2 $CaCl_2$, 1 $MgCl_2$, 92 CsCl, 10 glucose, 10 HEPES, pH 7.2.

Figure 7 shows that the human α_{1G} cDNA encodes a calcium channel with typical properties of a T-type current. The left panel illustrates representative current traces obtained from a holding potential of –100 mV to test pulses potentials of –90 mV to +20 mV. The traces show a typical crossover pattern and considerable inactivation during the test pulse, both of which are consistent with native T-type channels. The right panel shows a plot of the peak whole current at various test potentials and indicates that the human α_{1G} cDNA first activates near –60 mV with maximal current near –40 mV, which is also consistent with native low-threshold T-type calcium channels.

Claims

1. A DNA molecule which comprises an expression cassette wherein said expression cassette comprises a nucleotide sequence encoding a T-type calcium channel α_1 subunit, said encoding sequence operably linked to control sequences to effect its expression.

2. The DNA molecule of claim 1 wherein said α_1 subunit is α_{1G}, α_{1H}, or α_{1I}.

3. The DNA molecule of claim 2 wherein said α_1 subunit is derived from a mammal.

4. Recombinant host cells modified to contain the DNA molecule of any of claims 1-3.

5. The cells of claim 4 which are mammalian cells.

6. A method to effect production of a functional calcium channel which method comprises culturing the cells of claim 4 or 5 under conditions wherein said functional calcium channels are produced.

7. A method to identify a compound which is a modulator for T-type mammalian calcium channels, which method comprises contacting the cells employed in the method of claim 6 with said compound and assessing the effect of said compound on said cells.

8. A T-type calcium channel modulator identified by the method of claim 7.

9. A method to treat conditions characterized by undesirable levels of T-type calcium channel activity which method comprises administering to a subject in need of such treatment an effective amount of the modulator of claim 8.

10. The method of claim 9 wherein said condition is cardiac hypertrophy, cardiac arrythymia, hypertension, a sleep disorder, or epilepsy.

11. A DNA molecule which comprises an expression system for a nucleotide sequence which is complementary to the nucleotide sequence encoding a T-type calcium channel α_1 subunit or which forms a triple helix with DNA comprising said encoding sequence.

12. A method to treat a condition characterized by an undesirable level of T-type calcium channel activity which method comprises administering to a subject in need of such treatment an effective amount of the DNA molecule of claim 11.

13. The method of claim 12 wherein said condition is cardiac hypertrophy, cardiac arrythmia, hypertension, a sleep disorder, or epilepsy.

14. An oligonucleotide which consists essentially of a nucleotide sequence characteristic of a T-type calcium channel α_1 subunit, said oligonucleotide coupled to or comprising a detectable label.

15. A method to map the distribution of T-type calcium channels in a tissue which method comprises contacting said tissue with the oligonucleotide of claim 14.

16. Antibodies specifically immunoreactive with the extracellular portions of a T-type calcium channel.

17. A method to map the distribution of T-type calcium channels in a tissue which method comprises contacting said tissue with the antibodies of claim 16.

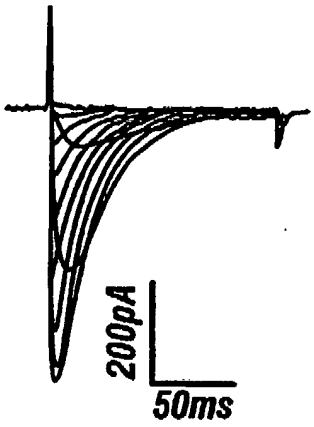


FIG. 1A

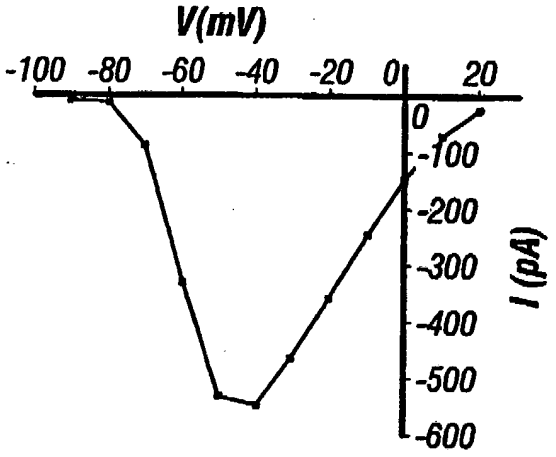


FIG. 1B

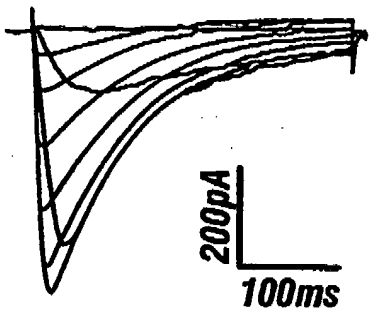


FIG. 2A

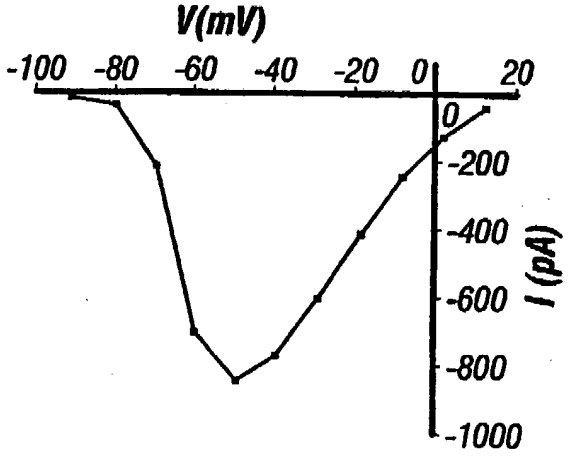


FIG. 2B

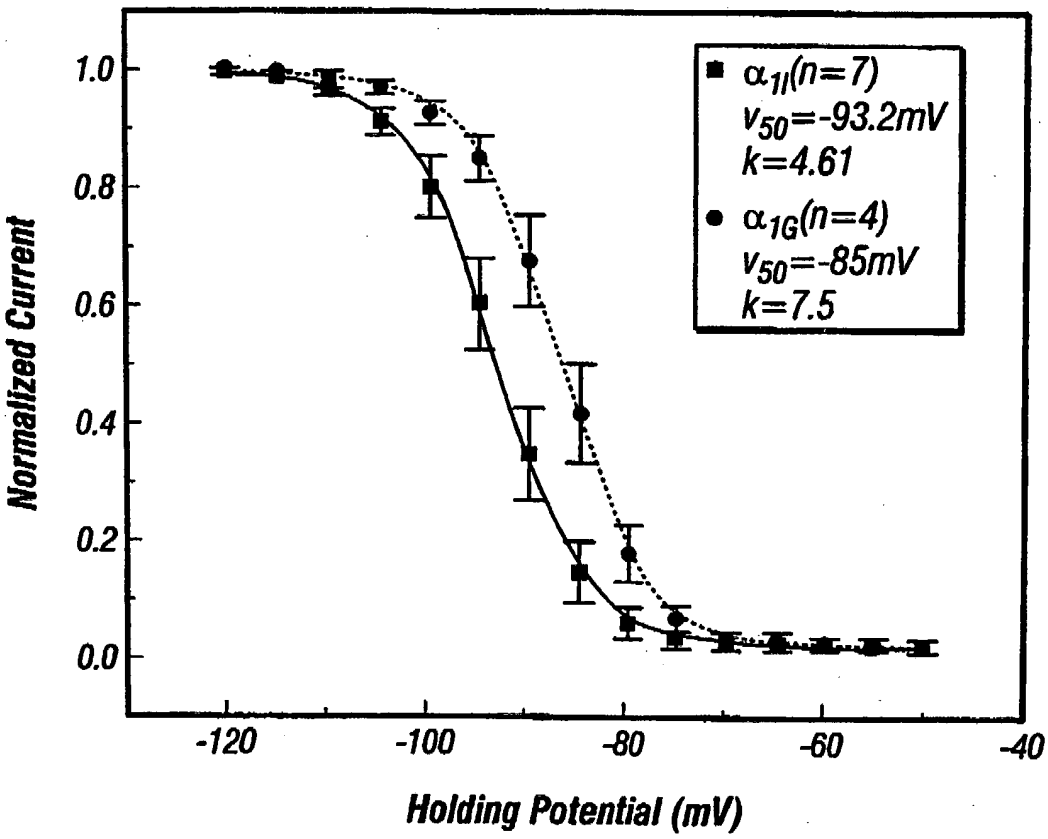

Normalized Current
1.0
0.8
0.6
0.4
0.2
0.0
-120
-100
-80
-60
-40
Holding Potential (mV)
α1I(n=7)
V50=-93.2mV
k=4.61
α1G(n=4)
V50=-85mV
k=7.5

FIG. 3

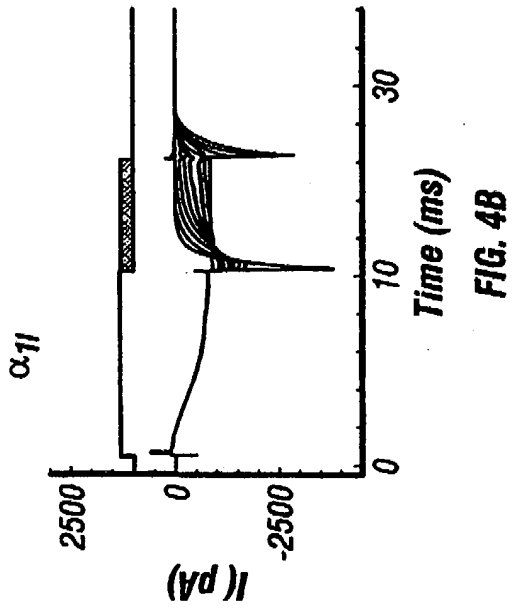


FIG. 4B

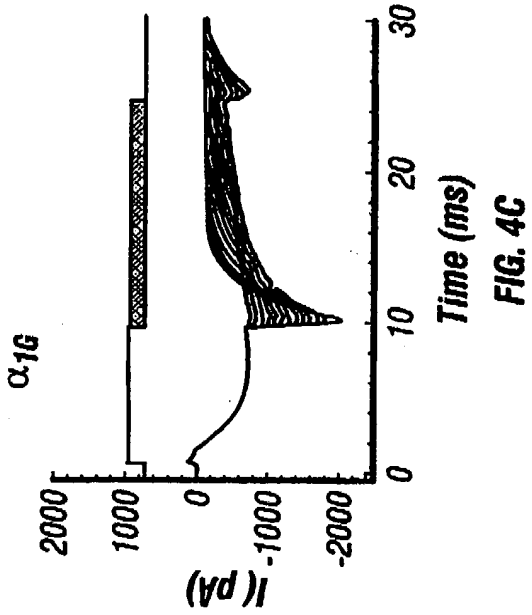


FIG. 4C

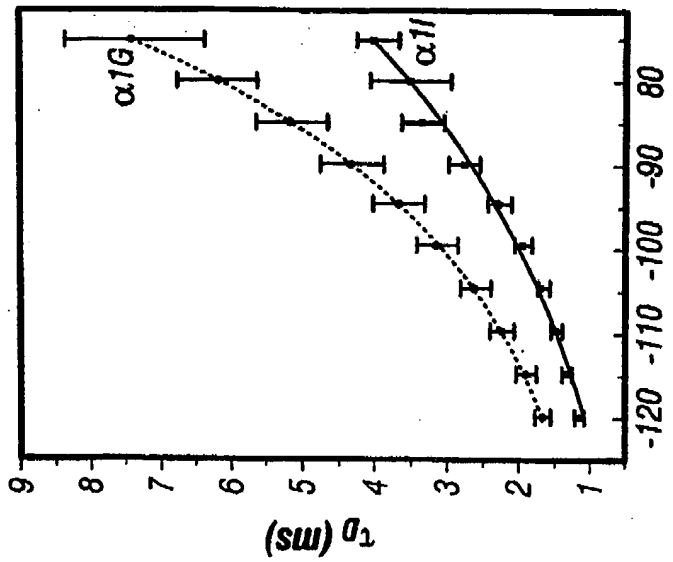
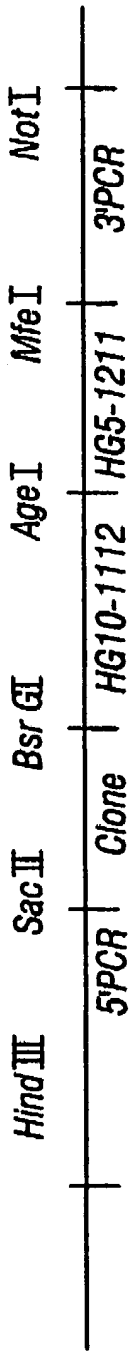


FIG. 4A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Sac II
Bsr GI
Age I
Mfe I
Not I
5'PCR
Clone
HG10-1112
HG5-1211
3'PCR

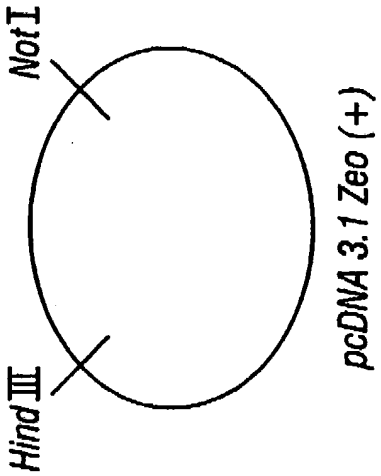
α1G
Not I
Hind III
pcDNA 3.1 Zeo (+)

FIG. 5A

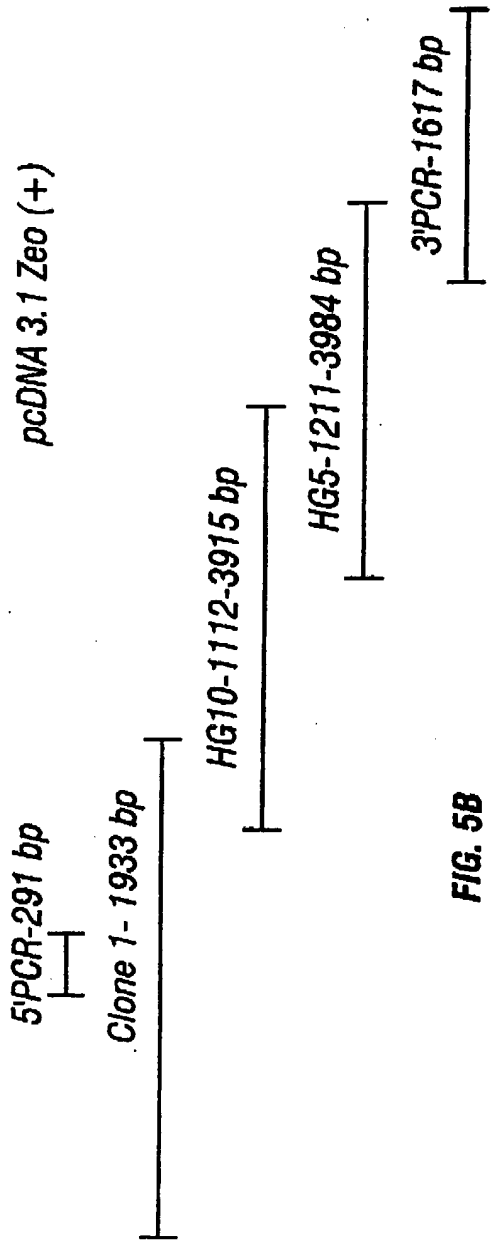
5'PCR-291 bp
Clone 1- 1933 bp
HG10-1112-3915 bp
HG5-1211-3984 bp
3'PCR-1617 bp

FIG. 5B

```
1 aagcttgcttgccccctctccggatcgcccgggggccccggctggccagagg ATG GAC GAG GAG GAT GGA   71
1                                                       M   D   E   E   E   D   G     7

72 GCG GGC GCC GAG GAG TCG GGA CAG CCC CGG AGC TTC ATG CGG CTC AAC GAC CTG TCG GGG 131
8 A   G   A   E   E   S   G   Q   P   R   S   F   M   R   L   N   D   L   S   G    27

132 GCC GGG GGC CGG CCG GGG TCA GCA GAA AAG GAC CCG GGC AGC GCG GAC TCC GAG 191
28 A   G   G   R   P   G   S   A   E   K   D   P   G   S   A   D   S   E    47

192 GCG GAG GGG CTG CCG TAC CCG GCG CTG GCC CCG GTG GTT TTC TTC TAC TTG AGC CAG GAC 251
48 A   E   G   L   P   Y   P   A   L   A   P   V   V   F   F   Y   L   S   Q   D    67

252 AGC CGC CCG CCG CGG AGC TGG TGT CTC CGC ACG GTC TGT AAC CCC TGG TTT GAG CGC ATC AGC 311
68 S   R   P   R   S   W   C   L   R   T   V   C   N   P   W   F   E   R   I   S    87

312 ATG TTG GTC ATC CTT CTC AAC TGC GTG ACC CTG GGC ATG TTC CGG CCA TGC GAG GAC ATC 371
88 M   L   V   I   L   L   N   C   V   T   L   G   M   F   R   P   C   E   D   I   107

372 GCC TGT GAC TCC CAG CGC TGC CGG ATC CTG CAG GCC TTT GAT GAC TTC ATC TTT GCC TTC 431
108 A   C   D   S   Q   R   C   R   I   L   Q   A   F   D   D   F   I   F   A   F   127

432 TTT GCC GTG GAG ATG GTG GTG AAG ATG GTG GCC TTG GGC ATC TTT GGG AAA AAG TGT TAC 491
128 F   A   V   E   M   V   V   K   N   V   A   L   G   I   F   G   K   K   C   Y   147

492 CTG GGA GAC ACT TGG AAC CGG CTT GAC TTT TTC ATC GTC ATC GCA GGG ATG CTG GAG TAC 551
148 L   G   D   T   N   N   R   L   D   F   F   I   V   I   A   G   M   L   E   Y   167

552 TCG CTG GAC CTG CAG AAC GTC AGC TTC TCA GCT GTC AGG ACA GTC CGT GTG CTG CGA CCG 611
168 S   L   D   L   Q   N   V   S   F   S   A   V   R   T   V   R   V   L   R   P   187
```

FIG. 6A

```
612 CTC AGG GCC ATT AAC CGG GTG CCC AGC ATG CGC ATC CTT GTC ACG TTG CTG CTG GAT ACG 671
188 L  R  A  I  N  R  V  P  S  M  R  I  L  V  T  L  L  L  D  T  207
672 CTG CCC ATG CTG GGC AAC GTC CTG CTG CTC TGC TTC TTC GTC TTC TTC ATC TTC GGC ATC 731
208 L  P  M  L  G  N  V  L  L  L  C  F  F  V  F  F  I  F  G  I  227
732 GTC GGC GTC CAG CTG TGG GCA GGG CTG CTT CGG AAC CGA TGC TTC CTA CCT GAG AAT TTC 791
228 V  G  V  Q  L  W  A  G  L  L  R  N  R  C  F  L  P  E  N  F  247
792 AGC CTC CCC CTG AGC GTG GAC CTG GAG CGC TAT TAC CAG ACA GAG AAC GAG GAT GAG AGC 851
248 S  L  P  L  S  V  D  L  E  R  Y  Y  O  T  E  N  E  D  E  S  267
852 CCC TTC ATC TGC TCC CAG CCA CGC GAG AAC GGC ATG CGG TCC TGC AGA AGC GTG CCC ACG 911
268 P  F  I  C  S  Q  P  R  E  N  G  M  R  S  C  R  S  V  P  T  287
912 CTG CGC GGG GAC GGG GGC GGT GGC CCA CCT TGC GGT CTG GAC TAT GAG GCC TAC AAC AGC 971
288 L  R  G  D  G  G  G  G  P  P  C  G  L  D  Y  E  A  Y  N  S  307
972 TCC AGC AAC ACC ACC TGT GTC AAC TGG AAC CAG TAC TAC ACC AAC TGC TCA GCG GGG GAG 1031
308 S  S  K  T  T  C  V  N  W  N  Q  Y  Y  T  N  C  S  A  G  E  327
1032 CAC AAC CCC TTC AAG GGC GCC ATC AAC TTT GAC AAC ATT GGC TAT GCC TGG ATC GCC ATC 1091
328 H  N  P  F  K  G  A  I  N  F  D  N  I  G  Y  A  W  I  A  I  347
1092 TTC CAG GTC ATC ACG CTG GAG GGC TGG GTC GAC ATC ATG TAC TTT GTG ATG GAT GCT CAT 1151
348 F  Q  V  I  T  L  E  G  W  V  D  I  M  Y  F  V  M  D  A  H  367
1152 TCC TTC TAC AAT TTC ATC TAC TTC ATC CTC CTC ATC ATC GTG GGC TCC TTC TTC ATG ATC 1211
368 S  F  Y  N  F  I  Y  F  I  L  L  I  I  V  G  S  F  F  M  I  387
```

FIG. 6B

```
1212 AAC CTG TGC CTG GTG GTG ATT GCC ACG CAG TTC TCA GAG ACC AAG CAG CGG GAA AGC CAG 1271
 388 N   L   C   L   V   V   I   A   T   Q   F   S   E   T   K   Q   R   E   S   Q   407
1272 CTG ATG CGG GAG CAG CGT GTG CGG TTC CTG TCC AAC GCC AGC ACC CTG GCT AGC TTC TCT 1331
 408 L   M   R   E   Q   R   V   R   F   L   S   N   A   S   T   L   A   S   F   S   427
1332 GAG CCC GGC AGC TGC TAT GAG GAG CTG CTC AAG TAC CTG GTG TAC ATC CTT CGT AAG GCA 1391
 428 E   P   G   S   C   Y   E   E   L   L   K   Y   L   V   Y   I   L   R   K   A   447
1392 GCC CGC AGG CTG GCT CAG GTC TCT CGG GCA GCA GGT GTG CGG GTT GGG CGT CTC AGC AGC 1451
 448 A   R   R   L   A   Q   V   S   R   A   A   G   V   R   V   G   L   L   S   S   467
1452 CCA GCA CCC CTC GGG GGC CAG GAG ACC CAG CCC AGC AGC AGC TGC TCT CGC TCC CAC CGC 1511
 468 P   A   P   L   G   G   Q   E   T   Q   P   S   S   S   C   S   R   S   H   R   487
1512 CGC CTA TCC GTC CAC CAC CTG GTG CAC CAC CAC CAC CAT CAC CAC CAC TAC CAC CTG 1571
 488 R   L   S   V   N   H   L   V   H   H   H   N   H   M   H   H   N   H   Y   H   L   507
1572 GGC AAT GGG ACG CTC AGG GCC CCC CGG GCC AGC CCG GAG ATC CAG GAC AGG GAT GCC AAT 1631
 508 G   N   G   T   L   R   A   P   R   A   S   P   E   I   Q   D   R   D   A   N   527
1632 GGG TCC CGC AGG CTC ATG CTG CCA CCA CCC TCG ACG CCT GCC CTC TCC GGG GCC CCC CCT 1691
 528 G   S   R   R   L   M   L   P   P   P   S   T   P   A   L   S   G   A   P   P   547
1692 GGT GGC GCA GAG TCT GTG CAC AGC TTC TAC CAT GCC GAC TGC CAC TTA GAG CCA GTC CGC 1751
 548 G   G   A   E   S   V   H   S   F   Y   H   A   D   C   M   L   E   P   V   R   567
1752 TGC CAG GCG CCC CCT CCC AGG TCC CCA TCT GAG GCA TCC GGC AGG ACT GTG GGC AGC GGG 1811
 568 C   Q   A   P   P   P   R   S   P   S   E   A   S   G   R   T   V   G   S   G   587
```

FIG. 6C

```
1812 AAG GTG TAT CCC ACC GTG CAC ACC AGC CCT CCA CCG GAG ACG CTG AAG GAG AAG GCA CTA 1871
 588 K   V   Y   P   T   V   N   T   S   P   P   P   E   T   L   K   E   R   A   L   607
1872 GTA GAG GTG GCT GCC AGC TCT GGG CCC CCA ACC CTC ACC AGC CTC AAC ATC CCA CCC GGG 1931
 608 V   E   V   A   A   S   S   G   P   P   T   L   T   S   L   N   I   P   P   G   627
1932 CCC TAC AGC TCC ATG CAC AAG CTG CTG GAG ACA CAG AGT ACA GGT GCC TGC CAA AGC TCT 1991
 628 P   Y   S   S   M   H   K   L   L   E   T   Q   S   T   G   A   C   Q   S   S   647
1992 TGC AAG ATC TCC AGC CCT TGC TTG AAA GCA GAC AGT GGA GCC TGT GGT CCA GAC AGC TGC 2051
 648 C   K   I   S   S   P   C   L   K   A   D   S   G   A   C   G   P   D   S   C   667
2052 CCC TAC TGT GCC CGG GCC GGG GCA GGG GAG GTG GAG CTC GCC GAC CGT GAA ATG CCT GAC 2111
 668 P   Y   C   A   R   A   G   A   G   E   V   E   L   A   D   R   E   M   P   D   687
2112 TCA GAC AGC GAG GCA GTT TAT GAG TTC ACA CAG GAT GCC CAG CAC AGC GAC CTC CGG GAC 2171
 688 S   D   S   E   A   V   Y   E   F   T   Q   D   A   Q   H   S   D   L   R   D   707
2172 CCC CAC AGC CGG CGG CAA CGG AGC CTG GGC CCA GAT GCA GAG CCC AGC TCT GTG CTG GCC 2231
 708 P   H   S   R   R   Q   R   S   L   G   P   D   A   E   P   S   S   V   L   A   727
2232 TTC TGG AGG CTA ATC TGT GAC ACC TTC CGA AAG ATT GTG GAC AGC AAG TAC TTT GGC CGG 2291
 728 F   W   R   L   I   C   D   T   F   R   K   I   V   D   S   K   Y   F   G   R   747
2292 GGA ATC ATG ATC GCC ATC CTG GTC AAC ACA CTC AGC ATG GGC ATC GAA TAC CAC GAG CAG 2351
 748 G   I   M   I   A   I   L   V   N   T   L   S   M   G   I   E   Y   H   E   Q   767
2352 CCC GAG GAG CTT ACC AAC GCC CTA GAA ATC AGC AAC ATC GTC TTC ACC AGC CTC TTT GCC 2411
 768 P   E   E   L   T   N   A   L   E   I   S   N   I   V   F   T   S   L   F   A   787
```

FIG. 6D

```
2412 CTG GAG ATG CTG CTG AAG CTG CTT GTG TAT GGT CCC TTT GGC TAC ATC AAG AAT CCC TAC 2471
 788 L  E  M  L  L  K  L  L  V  Y  G  P  F  G  Y  I  K  N  P  Y  807
2472 AAC ATC TTC GAT GGT GTC ATT GTG GTC ATC AGC GTG TGG GAG ATC GTG GGC CAG CAG GGG 2531
 808 N  I  F  D  G  V  I  V  V  I  S  V  N  E  I  V  G  Q  Q  G  827
2532 GGC GGC CTG TCG GTG CTG CGG ACC TTC CGC CTG ATG CGT GTG CTG AAG CTG GTG CGC TTC 2591
 828 G  G  L  S  V  L  R  T  F  R  L  M  R  V  L  K  L  V  R  F  847
2592 CTG CCG GCG CTG CAG CGG CAG CTG GTG CTC ATG AAG ACC ATG GAC AAC GTG GCC ACC 2651
 848 L  P  A  L  Q  R  Q  L  V  V  L  M  K  T  M  D  N  V  A  T  867
2652 TTC TGC ATG CTG CTT ATG CTC TTC ATC TTC ATC TTC AGC ATC CTG GGC ATG CAT CTC TTC 2711
 868 F  C  M  L  L  M  L  F  I  F  I  F  S  I  L  G  M  H  L  F  887
2712 GGC TGC AAG TTT GCC TCT GAG CGG GAT GGG GAC ACC CTG CCA GAC CGG AAG AAT TTT GAC 2771
 888 G  C  K  F  A  S  E  R  D  G  D  T  L  P  D  R  K  N  F  D  907
2772 TCC TTG CTC TGG GCC ATC GTC ACT GTC TTT CAG ATC CTG ACC CAG GAG GAC TGG AAC AAA 2831
 908 S  L  L  W  A  I  V  T  V  F  Q  I  L  T  Q  E  D  W  N  K  927
2832 GTC CTC TAC AAT GGT ATG GCC TCC ACG TCG TCC TGG GCG GCC CTT TAT TTC ATT GCC CTC 2891
 928 V  L  Y  N  G  M  A  S  T  S  S  W  A  A  L  Y  F  I  A  L  947
2892 ATG ACC TTC GGC AAC TAC GTG CTC TTC AAT TTG CTG GTC GCC ATT CTG GTG GAG GGC TTC 2951
 948 M  T  F  G  N  Y  V  L  F  N  L  L  V  A  I  L  V  E  G  F  967
2952 CAG GCG GAG GAA ATC AGC AAA CGG GAA GAT GCG AGT GGA CAG TTA AGC TGT ATT CAG CTG 3011
 968 Q  A  E  E  I  S  K  R  E  D  A  S  G  Q  L  S  C  I  Q  L  987
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FIG. 6E

```
3012 CCT GTC GAC TCC CAG GGG GGA GAT GCC AAC AAG TCC GAA TCA GAG CCC GAT TTC TTC TCA 3071
 988 P   V   D   S   Q   G   G   D   A   N   K   S   E   S   E   P   D   F   F   S   1007
3072 CCC AGC CTG GAT GGT GAT GGG GAC AGG AAG AAG TGC TTG GCC TTG GTG TCC CTG GGA GAG 3131
1008 P   S   L   D   G   D   G   D   R   K   K   C   L   A   L   V   S   L   G   E   1027
3132 CAC CCG GAG CTG CGG AAG AGC CTG CTG CCG CCT CTC ATC ATC CAC ACG GCC GCC ACA CCC 3191
1028 H   P   E   L   R   K   S   L   L   P   P   L   I   I   H   T   A   A   T   P   1047
3192 ATG TCG CTG CCC AAG AGC ACC AGC ACG GGC CTG GGC GAG GCG CTG GGC CCT GCG TCG CGC 3251
1048 M   S   L   P   K   S   T   S   T   G   L   G   E   A   L   G   P   A   S   R   1067
3252 CGC ACC AGC AGC AGC GGG TCG GCA GAG CCT GGG GCG GCC CAC GAG ATG AAG TCA CCG CCC 3311
1068 R   T   S   S   S   G   S   A   E   P   G   A   A   H   E   M   K   S   P   P   1087
3312 AGC GCC CGC AGC TCT CCG CAC AGC CCC TGG AGC GCT GCA AGC AGC TGG ACC AGC AGG CGC 3371
1088 S   A   R   S   S   P   H   S   P   W   S   A   A   S   S   W   T   S   R   R   1107
3372 TCC AGC CGG AAC AGC CTC GGC CGT GCA CCC AGC CTG AAG CGG AGA AGC CCA AGT GGA GAG 3431
1108 S   S   R   N   S   L   G   R   A   P   S   L   K   R   R   S   P   S   G   E   1127
3432 CGG CGG TCC CTG TTG TCG GGA GAA GGC CAG GAG AGC CAG GAT GAA GAG GAG AGC TCA GAA 3491
1128 R   R   S   L   L   S   G   E   G   Q   E   S   Q   D   E   E   E   S   S   E   1147
3492 GAG GAG CGG GCC AGC CCT GCG GGC AGT GAC CAT CGC CAC AGG GGG TCC CTG GAG CGG GAG 3551
1148 E   E   R   A   S   P   A   G   S   D   H   R   N   R   G   S   L   E   R   E   1167
3552 GCC AAG AGT TCC TTT GAC CTG CCA GAC ACA CTG CAG CTG CCA GGG CTG CAT CGC ACT GCC 3611
1168 A   K   S   S   F   D   L   P   D   T   L   Q   V   P   G   L   H   R   T   A   1187
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FIG. 6F

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3612 AGT GGC CGA GGG TCT GCT TCT GAG CAC CAG GAC TGC AAT CGC AAG TCG GCT TCA GGG CGC 3671
1188 S   G   R   G   S   A   S   E   H   Q   D   C   N   G   K   S   A   S   G   R   1207
3672 CTG GCC CGG GCC CTG CGG CCT GAT GAC CCC CCA CTG GAT GGG GAT GAC GCC GAT GAC GAG 3731
1208 L   A   R   A   L   R   P   D   D   P   P   L   D   G   D   D   A   D   D   E   1227
3732 GGC AAC CTG AGC AAA GGG GAA CGG GTC CGC GCG TGG ATC CGA GCC CGA CTC CCT GCC TGC 3791
1228 G   N   L   S   K   G   E   R   V   R   A   W   I   R   A   R   L   P   A   C   1247
3792 TAC CTC GAG CGA GAC TCC TGG TCA CCC TAC ATC TTC CCT CCT CAG TCC AGG TTC CGC CTC 3851
1248 Y   L   E   R   D   S   W   S   A   Y   I   F   P   P   Q   S   R   F   R   L   1267
3852 CTG TGT CAC CGG ATC ATC ACC CAC AAG ATG TTC GAC CAG GTG GTC CTT GTC ATC ATC TTC 3911
1268 L   C   H   R   I   I   T   N   K   M   F   D   H   V   V   L   V   I   I   F   1287
3912 CTT AAC TGC ATC ACC ATC GCC ATG GAG CGC CCC AAA ATT GAC CCC CAC AGC GCT GAA CGC 3971
1288 L   N   C   I   T   I   A   M   E   R   P   K   I   D   P   H   S   A   E   R   1307
3972 ATC TTC CTG ACC CTC TCC AAT TAC ATC TTC ACC GCA GTC TTT CTG GCT GAA ATG ACA GTG 4031
1308 I   F   L   T   L   S   N   Y   I   F   T   A   V   F   L   A   E   M   T   V   1327
4032 AAG GTG GTG GCA CTG GGC TGG TGC TTC GGG GAG CAG GCG TAC CTG CGG AGC AGT TGG AAC 4091
1328 K   V   V   A   L   G   W   C   F   G   E   Q   A   Y   L   R   S   S   W   N   1347
4092 GTG CTG GAC GGG CTG TTG GTG CTC ATC TCC GTC ATC GAC ATT CTG GTG TCC ATG GTC TCT 4151
1348 V   L   D   G   L   L   V   L   I   S   V   I   D   I   L   V   S   M   V   S   1367
4152 GAC AGC GGC ACC AAG ATC CTG GGC ATG CTG AGG GTG CTG CGG CTG CTG CGG ACC CTG CGC 4211
1368 D   S   G   T   K   I   L   G   M   L   R   V   L   R   L   L   R   T   L   R   1387
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FIG. 6G

SUBSTITUTE SHEET (RULE 26)

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4212 CCG CTC AGG GTG ATC AGC CGG GCG CAG GGG CTG AAG CTG GTG GTG GAG ACG CTG ATG TCC 4271
1388 P   L   R   V   I   S   R   A   Q   G   L   K   L   V   V   E   T   L   M   S   1407
4272 TCA CTG AAA CCC ATC GGC AAC ATT GTA GTC ATC TGC TGT GCC TTC TTC ATC ATT TTC GGC 4331
1408 S   L   K   P   I   G   N   I   V   V   I   C   C   A   F   F   I   I   F   G   1427
4332 ATC TTG GGG GTG CAG CTC TTC AAA GGG AAG TTT TTC GTG TGC CAG GGC GAG GAT ACC AGG 4391
1428 I   L   G   V   Q   L   F   K   G   K   F   F   V   C   Q   G   E   D   T   R   1447
4392 AAC ATC ACC AAT AAA TCG GAC TGT GCC GAG GCC AGT TAC CGG TGG GTC CGG CAC AAG TAC 4451
1448 N   I   T   N   K   S   D   C   A   E   A   S   Y   R   W   V   R   M   K   Y   1467
4452 AAC TTT GAC AAC CTT GGC CAG GCC CTG ATG TCC CTG TTC GTT TTG GCC TCC AAG GAT GGT 4511
1468 N   F   D   N   L   G   Q   A   L   M   S   L   F   V   L   A   S   K   D   G   1487
4512 TGG GTG GAC ATC ATG TAC GAT GGG CTG GAT GCT GTG GGC GTG GAC CAG CAG CCC ATC ATG 4571
1488 W   V   D   I   M   Y   D   G   L   D   A   V   G   V   D   Q   Q   P   I   M   1507
4572 AAC CAC AAC CCC TGG ATG CTG CTG TAC TTC ATC TCG TTC CTG CTC ATT GTG GCC TTC TTT 4631
1508 N   H   N   P   N   M   L   L   Y   F   I   S   F   L   L   I   V   A   F   F   1527
4632 GTC CTG AAC ATG TTT GTG GGT GTG GTG GTG GAG AAC TTC CAC AAG TGT AGG CAG CAC CAG 4691
1528 V   L   N   M   F   V   G   V   V   V   E   N   F   H   K   C   R   Q   H   Q   1547
4692 GAG GAA GAG GAG GCC CGG CGG CGG GAG GAG AAG CGC CTA CGA AGA CTG GAG AAA AAG AGA 4751
1548 E   E   E   E   A   R   R   R   E   E   K   R   L   R   R   L   E   K   K   R   1567
4752 AGG AAA GCC CAG TGC AAA CCT TAC TAC TCC GAC TAC TCC CGC TTC CGG CTC CTC GTC CAC 4811
1568 R   K   A   Q   C   K   P   Y   Y   S   D   Y   S   R   F   R   L   L   V   H   1587
```

FIG. 6H

```
4812 CAC TTG TGC ACC AGC CAC TAC CTG GAC CTC TTC ATC ACA GGT GTC ATC GGG CTG AAC GTG 4871
1588 H   L   C   T   S   H   Y   L   D   L   F   I   T   G   V   I   G   L   N   V   1607
4872 GTC ACC ATG GCC ATG GAG CAC TAC CAG CAG CCC CAG ATT CTG GAT GAG GCT CTG AAG ATC 4931
1608 V   T   M   A   M   E   H   Y   Q   Q   P   Q   I   L   D   E   A   L   K   I   1627
4932 TGC AAC TAC ATC TTC ACT GTC ATC TTT GTC TTG GAG TCA GTT TTC AAA CTT GTG GCC TTT 4991
1628 C   N   Y   I   F   T   V   I   F   V   L   E   S   V   F   K   L   V   A   F   1647
4992 GGT TTC CGT CGG TTC TTC CAG GAC AGG TGG AAC CAG CTG GAC CTG GCC ATT GTG CTG CTG 5051
1648 G   F   R   R   F   F   Q   D   R   W   N   Q   L   D   L   A   I   V   L   L   1667
5052 TCC ATC ATG GGC ATC ACG CTG GAG GAA ATC GAG GTC AAC GCC TCG CTG CCC ATC AAC CCC 5111
1668 S   I   M   G   I   T   L   E   E   I   E   V   N   A   S   L   P   I   N   P   1687
5112 ACC ATC ATC CGC ATC ATG AGG GTG CTG CGC ATT GCC CGA GTG CTG AAG CTG CTG AAG ATG 5171
1688 T   I   I   R   I   M   R   V   L   R   I   A   R   V   L   K   L   L   K   M   1707
5172 GCT GTG GGC ATG CGG GCG CTG CTG GAC ACG GTG ATG CAG GCC CTG CCC CAG GTG GGG AAC 5231
1708 A   V   G   M   R   A   L   L   D   T   V   M   Q   A   L   P   Q   V   G   N   1727
5232 CTG GGA CTT CTC TTC ATG TTG TTG TTT TTC ATC TTT GCA GCT CTG GGC GTG GAG CTC TTT 5291
1728 L   G   L   L   F   M   L   L   F   F   I   F   A   A   L   G   V   E   L   F   1747
5292 GGA GAC CTG GAG TGT GAC GAG ACA CAC CCC TGT GAG GGC CTG GGC CGT CAT GCC ACC TTT 5351
1748 G   D   L   E   C   D   E   T   H   P   C   E   G   L   G   R   H   A   T   F   1767
5352 CGG AAC TTT GGC ATG GCC TTC CTA ACC CTC TTC CGA GTC TCC ACA GGT GAC AAT TGG AAT 5411
1768 R   N   F   G   M   A   F   L   T   L   F   R   V   S   T   G   D   N   W   E   1787
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FIG. 6I

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5412	GGC	ATT	ATG	AAG	GAC	ACC	CTC	CGG	GAC	TGT	GAC	CAG	GAG	TCC	ACC	TGC	TAC	AAC	ACG	GTC	5471
1788	G	I	M	K	D	T	L	R	D	C	D	Q	E	S	T	C	Y	F	T	V	1807
5472	ATC	TCG	CCT	ATC	TAC	TTT	GTG	TCC	TTC	GTG	CTG	ACG	GCC	CAG	TTC	GTG	CTA	GTC	AAC	GTG	5531
1808	I	S	P	I	Y	F	V	S	F	V	L	T	A	Q	F	V	L	V	M	V	1827
5532	GTG	ATC	GCC	GTG	CTG	ATG	AAG	CAC	CTG	GAG	GAG	AGC	AAC	AAG	GAG	GCC	AAG	GAG	GAG	GCC	5591
1828	V	I	A	V	L	M	K	H	L	E	E	S	N	K	E	A	K	E	E	A	1847
5592	GAG	CTA	GAG	GCT	GAG	CTG	GAG	CTG	GAG	ATG	AAG	ACC	CTC	AGC	CCC	CAG	CCC	CAC	TCG	CCA	5651
1848	E	L	E	A	E	L	E	L	E	M	K	T	L	S	P	Q	P	H	S	P	1867
5652	CTG	GGC	AGC	CCC	TTC	CTC	TGG	CCT	GGG	GTC	GAG	GGC	CCC	GAC	AGC	CCC	GAC	AGC	CCC	AAG	5711
1868	L	G	S	P	F	L	N	P	G	V	E	G	P	D	S	P	D	S	P	K	1887
5712	CCT	GGG	GCT	CTG	CAC	CCA	GCG	GCC	CAC	GCG	AGA	TCA	GCC	TCC	CAC	TTT	TCC	CTG	GAG	CAC	5771
1888	P	G	A	L	M	P	A	A	H	A	R	S	A	S	H	F	S	L	E	H	1907
5772	CCC	ACG	ATG	CAG	CCC	CAC	CCC	ACG	GAG	CTG	CCA	GGA	CCA	GAC	TTA	CTG	ACT	GTG	CGG	AAG	5831
1908	P	T	M	Q	P	H	P	T	E	L	P	G	P	D	L	L	T	V	R	K	1927
5832	TCT	GGG	GTC	AGC	CGA	ACG	CAC	TCT	CTG	CCC	AAT	GAC	AGC	TAC	ATG	TGT	CGG	CAT	GGG	AGC	5891
1928	S	G	V	S	R	T	M	S	L	P	N	D	S	Y	M	C	R	R	G	S	1947
5892	ACT	GCC	GAG	GGG	CCC	CTG	GGA	CAC	AGG	GGC	TGG	GGG	CTC	CCC	AAA	GCT	CAG	TCA	GGC	TCC	5951
1948	T	A	E	G	P	L	G	H	R	G	W	G	L	P	K	A	Q	S	G	S	1967
5952	GTC	TTG	TCC	GTT	CAC	TCC	CAG	CCA	GCA	GAT	ACC	AGC	TAC	ATC	CTG	CAG	CTT	CCC	AAA	GAT	6011
1968	V	L	S	V	H	S	Q	P	A	D	T	S	Y	I	L	Q	L	P	K	D	1987

FIG. 6J

```
6012 GCA CCT CAT CTG CTC CAG CCC CAC AGC GCC CCA ACC TGG GGC ACC ATC CCC AAA CTG CCC 6071
1988 A   P   H   L   L   Q   P   M   S   A   P   T   W   G   T   I   P   K   L   P   2007
6072 CCA CCA GGA CGC TCC CCT TTG GCT CAG AGG CCA CTC AGG CGC CAG GCA GCA ATA AGG ACT 6131
2008 P   P   G   R   S   P   L   A   Q   R   P   L   R   R   Q   A   A   I   R   T   2027
6132 GAC TCC TTG GAC GTT CAG GGT CTG GGC AGC CGG GAA GAC CTG CTG GCA GAG GTG AGT GGG 6191
2028 D   S   L   D   V   Q   G   L   G   S   R   E   D   L   L   A   E   V   S   G   2047
6192 CCC TCC CCG CCC CTG GCC CGG GCC TAC TCT TTC TGG GGC CAG TCA AGT ACC CAG GCA CAG 6251
2048 P   S   P   P   L   A   R   A   Y   S   F   W   G   Q   S   S   T   Q   A   Q   2067
6252 CAG CAC TCC CGC AGC CAC AGC AAG ATC TCC AAG CAC ATG ACC CCG CCA GCC CCT TGC CCA 6311
2068 Q   H   S   R   S   H   S   K   I   S   K   H   H   T   P   P   A   P   C   A   2087
6312 GGC CCA GAA CCC AAC TGG GGC AAG GGC CCT CCA GAG ACC AGA AGC AGC TTA GAG TTG GAC 6371
2088 G   P   E   P   N   M   G   K   G   P   P   E   T   R   S   S   L   E   L   D   2107
6372 ACG GAG CTG AGC TGG ATT TCA GGA GAC CTC CTG CCC CCT GGC GGC CAG GAG GAG CCC CCA 6431
2108 T   E   L   S   N   I   S   G   D   L   L   P   P   G   G   Q   E   E   P   P   2127
6432 TCC CCA CGG GAC CTG AAG AAG TGC TAC AGC GTG GAG GCC CAG AGC TGC CAG CGC CGG CCT 6491
2128 S   P   R   D   L   K   K   C   Y   S   V   E   A   Q   S   C   Q   R   R   P   2147
6492 ACG TCC TGG CTG GAT GAG CAG AGG AGA CAC TCT ATC GCC GTC AGC TGC CTG GAC AGC GGC 6551
2148 T   S   W   L   D   E   Q   R   R   H   S   I   A   V   S   C   L   D   S   G   2167
6552 TCC CAA CCC CAC CTG GGC ACA GAC CCC TCT AAC CTT GGG GGC CAG CCT CTT GGG GGG CCT 6611
2168 S   Q   P   H   L   G   T   D   P   S   N   L   G   G   Q   P   L   G   G   P   2187
```

FIG. 6K

SUBSTITUTE SHEET (RULE 26)

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6612 GGG AGC CGG CCC AAG AAA AAA CTC AGC CCG CCT AGT ATC ACC ATA GAC CCC CCC GAG AGC  6671
2188 G   S   R   P   K   K   K   L   S   P   P   S   I   T   I   D   P   P   E   S    2207
6672 CAA GGT CCT CGG ACC CCG CCC AGC CCT GGT ATC TGC CTC CGG AGG AGG GCT CCG TCC AGC  6731
2208 Q   G   P   R   T   P   P   S   P   G   I   C   L   R   R   R   A   P   S   S    2227
6732 GAC TCC AAG GAT CCC TTG GCC TCT GGC CCC CCT GAC AGC ATG GCT GCC TCG CCC TCC CCA  6791
2228 D   S   K   D   P   L   A   S   G   P   P   D   S   M   A   A   S   P   S   P    2247
6792 AAG AAA GAT GTG CTG AGT CTC TCC GGT TTA TCC TCT GAC CCA GCA GAC CTG GAC CCC TGA  6851
2248 K   K   D   V   L   S   L   S   G   L   S   S   D   P   A   D   L   D   P   -    2267
6852 gtcctgccccactttcccactcaccttctccactgggtgc                                      6892
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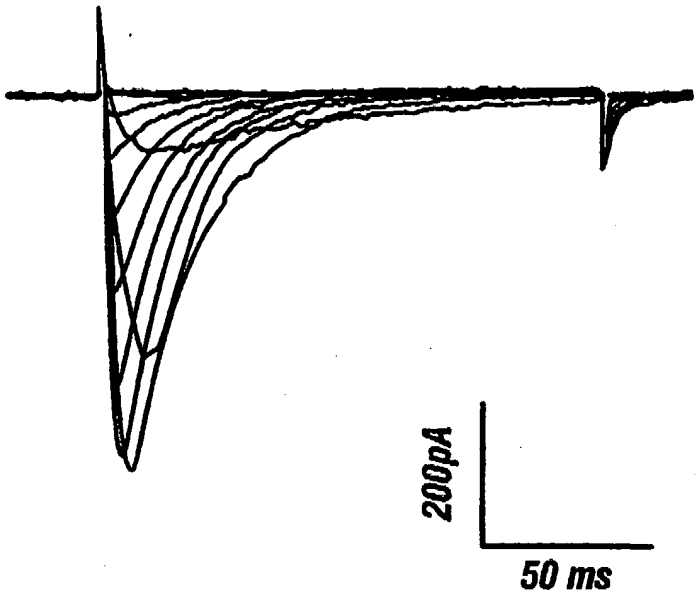
FIG. 6L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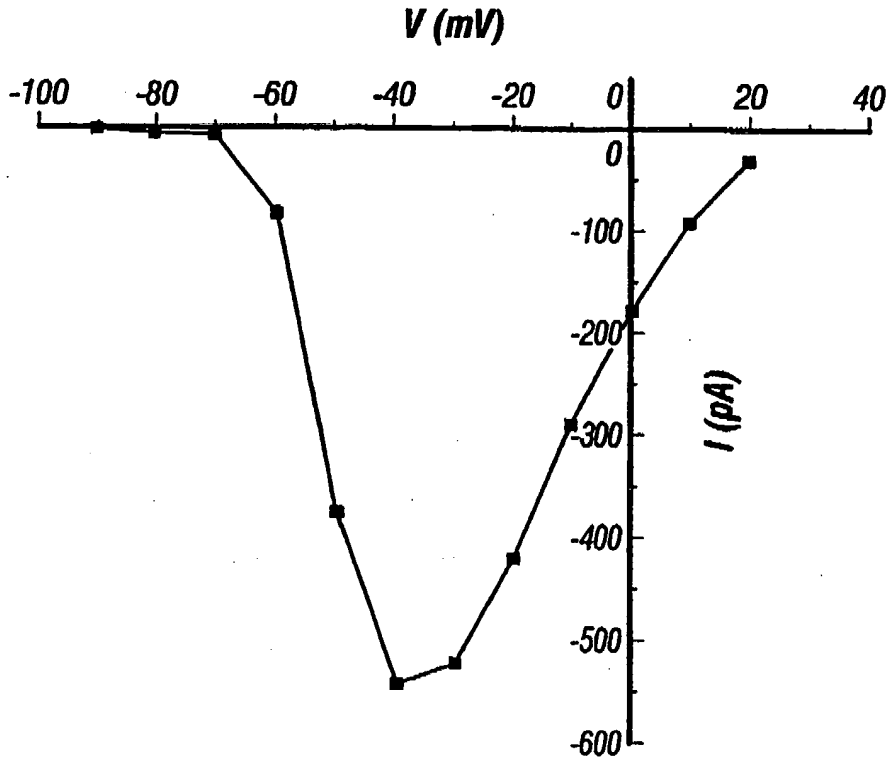
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-400
-500
-600
I (pA)

FIG. 7

I			II			III			IV			
LAASE	E	GWVYV	QIITQ	E	GWTDF	ETLSF	K	GWNVI	RCLTG	E	DWNDI	*NIC-1 (C11D2.6)*
LAASQ	E	GWVYV	QIITQ	E	GWTDV	ETLSY	K	GWNVV	RSVTG	E	DWNDI	*NIC-2 (C27F2.3)*
EASSQ	E	GWVFL	QILTQ	E	GWVDV	EVLSL	K	GWVEV	RIVTG	E	DWNKI	*Rat -NIC*
QCITM	E	GWTDV	QILTG	E	DWNSV	TVSTF	K	GWPEL	RCATG	E	AWQDI	*L-Type Ca Channel*
QVITL	E	GWVDI	QILTQ	E	DWNKV	VLASK	D	GWVDI	RVSTG	D	NWNGI	*T-Type Ca Channel*
RLMTQ	D	FWENL	RVLCG	E	WIETM	QVATF	K	GWMDI	QITTS	A	GWDGL	*Na Channels*

FIG. 8

SEQUENCE LISTING

<110> Snutch, Terry P.
Baillie, David L.

<120> NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

<130> NMED.P-001-2(CIP)

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Gly Lys Tyr Tyr Thr Gln Gly Asp Lys Val Leu Met Pro Leu Ala Ile
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Gln Ala Leu Lys Gln Leu Met Phe Lys Leu Val Ala Thr Val Ala Arg
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Thr His Ala Thr Pro Ser His Ile Thr Gly Gly Pro Gly Thr Gly Met
 65                  70                  75                  80

His Thr Gly Thr Phe Gln Glu Gly Ala Glu Pro Gly Ser Ser Gln His
                85                  90                  95

Pro Glu Ala Gln Ala Thr Tyr Thr Ala Gly Cys Thr Pro Ala Pro Thr
            100                 105                 110

Gly Asp Pro Thr Cys Cys Phe Val Leu Asp Leu Val Cys Thr Trp Phe
        115                 120                 125

Glu Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly
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Met Tyr Gln Pro Cys Asp Asp Met Asp Cys Leu Ser Asp Arg Cys Lys
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Ile Leu Gln Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu
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Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly
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Asn Ile Asn Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu
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Lys Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Asn Leu Leu
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370 375 380

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385 390 395 400

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420 425 430

Ser Phe Ser Thr Ala Gln Ser Pro Lys Cys Gln Gly Asp Ser Leu Pro
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Gly Val Ala Ala Glu Ser Leu Leu Leu Arg Asp Ser Ser Ser Ser Val
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Ile Thr Asp Glu Ala Ala Ala Met Glu Asn Leu Leu Ala Gly Thr Ser
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Lys Gly Asp Glu Ser Tyr Leu Leu Arg Leu Ala Gly Ser Gln Val His
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Ser Gln Ala Gln Gln Met Leu Gly Arg Gly Leu Gly Pro Glu Ser Leu
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Glu Thr Gly Glu Glu Pro His Ser Trp Ser Pro Arg Ala Thr Arg Arg
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Trp Asp Pro Gln Cys Gln Pro Gly Gln Pro Leu Pro Leu His Phe Met
530 535 540

Gln Ala Gln Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val

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Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu His Arg Leu Met
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Leu Glu Gln Arg Gln Arg Tyr Leu Ser Ser Ser Thr Val Ala Ser Tyr
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Ala Glu Pro Gly Asp Cys Tyr Glu Glu Ile Phe Gln Tyr Val Cys His
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Ile Leu Arg Lys Ala Lys Arg Arg Ala Leu Gly Leu Tyr Gln Ala Leu
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Gln Ser Arg Arg Gln Ala Leu Gly Pro Glu Ala Pro Ala Pro Ala Lys
625                 630                 635                 640

Pro Gly Pro His Ala Lys Glu Pro Arg His Tyr Pro Leu Thr Val Trp
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Glu Ser Ile Leu Gly Arg Gln Ala Glu Glu Cys Thr Leu Arg Ala Ala
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Ala His Pro Ser Ser Gly Ala Ser His Pro Gly Val Gly Ser Glu Glu
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Ala Pro Glu Leu Cys Pro Gln His Ser Pro Leu Asp Ala Thr Pro His
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Thr Leu Val Gln Pro Ile Pro Ala Thr Leu Ala Ser Asp Pro Ala Ser
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Cys Pro Cys Cys Gln His Glu Asp Gly Arg Arg Pro Ser Gly Leu Gly
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Ser Thr Asp Ser Gly Gln Glu Gly Ser Gly Ser Gly Ser Ser Ala Gly
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Gly Glu Asp Glu Ala Asp Gly Asp Gly Ala Arg Ser Ser Glu Asp Gly
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Ala Ser Ser Glu Leu Gly Lys Glu Glu Glu Glu Glu Glu Gln Ala Asp
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Gly Ala Val Trp Leu Cys Gly Asp Val Trp Arg Glu Thr Arg Ala Lys
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Leu Arg Gly Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met
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Ala Ile Leu Val Asn Thr Val Ser Met Gly Ile Glu His His Glu Gln
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Ala Ser Ala Ala Gln Pro Gly Arg Ala Cys Gly Arg Gly Gln Asn Pro
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Asp Leu Cys Met Thr Leu Lys Ala Pro Cys Leu Cys His Asn Val Pro
850 855 860

Ser Pro Gly Gln Gly Val Leu Ser His Pro Val Thr Pro Pro His Thr
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Ala Pro Trp Arg Met Glu Thr Gly Lys Gln Gly His Gly Cys Glu Glu
885 890 895

Gly Pro Gly Gln Arg Ser Ser Asp Met Phe Ala Leu Glu Met Ile Leu
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Lys Leu Ala Ala Phe Gly Leu Phe Asp Tyr Leu Arg Asn Pro Tyr Asn
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Ile Phe Asp Ser Ile Ile Val Ile Ile Ser Ile Trp Glu Ile Val Gly
930 935 940

Gln Ala Asp Gly Gly Leu Ser Val Leu Arg Thr Phe Arg Leu Leu Arg
945 950 955 960

Val Leu Lys Leu Val Arg Phe Met Pro Ala Leu Arg Arg Gln Leu Val
965 970 975

Val Leu Met Lys Thr Met Asp Asn Val Ala Thr Phe Cys Met Leu Leu
980 985 990

Met Leu Phe Ile Phe Ile Phe Ser Ile Leu Gly Met His Ile Phe Gly
995 1000 1005

Cys Lys Phe Ser Leu Arg Thr Asp Thr Gly Asp Thr Val Pro Asp Arg
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Lys Asn Phe Asp Ser Leu Leu Trp Ala Ile Val Thr Val Phe Gln Ile
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Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly Met Ala Ser
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Thr Ser Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met Thr Phe Gly

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Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val Glu Gly Phe
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Gln Ala Glu Val Thr Val Val Leu Ala Glu Glu Ala Pro Pro Gln Gly
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Asp Glu Val Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser
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Ser Ser Asn Ile Glu Glu Phe Asp Lys Leu Gln Glu Gly Leu Asp Ser
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Leu Asp Pro Ser Leu Pro Leu Gly Gly His Leu Gly Pro Ala Gly Ala
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Ala Gly Pro Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro Met Leu Val
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Ala Leu Gly Ser Arg Lys Ser Ser Val Met Ser Leu Gly Arg Met Ser
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Tyr Asp Gln Arg Ser Leu Val Gly Gly Leu Arg Ala Thr Ala Gly Val
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Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp Ala Ser Arg Arg Ser
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Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser
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Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg Val Cys Glu Val Ala

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Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu His Thr Pro His Ala
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His His Val His His Gly Pro His Leu Ala His Arg His Arg His His
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Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser Val Asp Leu Ala Glu
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Leu Val Pro Ala Val Gly Ala His Pro Arg Ala Ala Trp Arg Ala Ala
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Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly Arg Met Pro Ser Ile
1395 1400 1405

Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg Gly Asp Arg Gly Glu
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Asp Glu Glu Glu Ile Asp Tyr Val Ser Gly Gly Gly Ala Glu Gly Asp
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Leu Thr Leu Cys Phe Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro
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Asp Trp Cys Glu Val Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro
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Glu Asn Arg Leu Arg Asp Leu Gly Trp Val Ser Leu Glu Cys Gln Gly
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Lys Val Gly Asp Leu Val Val Trp Val Tyr Gly Gln Arg Arg Gln Arg
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Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe
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Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val Ser Leu Gly
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Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu

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Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val Val Ser Leu
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Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Leu Arg
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Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro Gly
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Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly
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Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
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Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp
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Thr Arg Asn Ile Thr Asn Arg Ser Asp Cys Met Ala Ala Asn Tyr Arg
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Trp Val His His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
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Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asn Ile Met Tyr
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Asn Gly Leu Asp Ala Val Ala Val Asp Gln Gln Pro Val Thr Asn His
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Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ser
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Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
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Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu Glu
1780 1785 1790

Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Arg Leu
1795 1800 1805

Pro Tyr Tyr Ala Thr Tyr Cys His Thr Arg Leu Leu Ile His Ser Met
1810 1815 1820

Cys Thr Ser His Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile Cys Leu

1825 1830 1835 1840

Asn Val Val Thr Met Ser Leu Glu His Tyr Asn Gln Pro Thr
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<212> DNA
<213> HUMAN

<220>
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<213> HUMAN

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Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
35 40 45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
50 55 60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Ser Gly Asp

65 70 75 80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
85 90 95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
100 105 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
115 120 125

Tyr Asn Val Cys Arg Thr Gly Ser Ala Asn Pro His Lys Gly Ala Ile
130 135 140

Ser Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145 150 155 160

Thr Leu Glu Gly Trp Val Ala Ile Met Tyr Tyr Val Met Asp Ala Leu
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Ser Phe Tyr Asn Phe Val Tyr Phe Ile Leu Leu Ile Ile
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<212> DNA
<213> rat

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<212> PRT
<213> rat

<220>
<223> rat alpha-I partial sequence

<400> 22

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Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
         35                  40                  45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
     50                  55                  60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
 65                  70                  75                  80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
                 85                  90                  95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
            100                 105                 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
        115                 120                 125

Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
    130                 135                 140

Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145                 150                 155                 160

Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
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Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
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<400> 23

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Pro Val Ala Ser Arg Ser Ser Thr Thr Cys Pro Gly Pro Gly Ala Ala
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Gly Ala Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
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Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
                 85                  90                  95

Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
            100                 105                 110

Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val
        115                 120                 125

Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
    130                 135                 140

Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
145                 150                 155                 160

Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
                165                 170                 175

Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
            180                 185                 190

Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
        195                 200                 205

Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
    210                 215                 220

Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu
225                 230                 235                 240

Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile
                245                 250                 255

Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg
            260                 265                 270

Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu
        275                 280                 285

Pro Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser
    290                 295                 300

Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu
305                 310                 315                 320
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Arg Gly Glu Gly Gly Gly Gly Pro Pro Cys Ser Leu Asp Tyr Glu Thr
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Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr
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Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn
        355                 360                 365

Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
    370                 375                 380

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
385                 390                 395                 400

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
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Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
            420                 425                 430

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
        435                 440                 445

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
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Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
465                 470                 475                 480

Arg Arg Leu Ala Gln Val Ser Arg Ala Ile Gly Val Arg Ala Gly Leu
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Leu Ser Ser Pro Val Ala Arg Ser Gly Gln Glu Pro Gln Pro Ser Gly
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Ser Cys Thr Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
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His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
    530                 535                 540

Arg Val Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly
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Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Thr Pro Ser Gly
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Gly Pro Pro Arg Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp
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Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Cys Pro
        595                 600                 605

Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr
    610                 615                 620

Val His Thr Ser Pro Pro Pro Glu Ile Leu Lys Asp Lys Ala Leu Val
625                 630                 635                 640

Glu Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile
                645                 650                 655

Pro Pro Gly Pro Phe Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser
            660                 665                 670

Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys
        675                 680                 685

Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg
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Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser
705                 710                 715                 720

Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp
                725                 730                 735

Leu Arg Asp Pro His Ser Arg Arg Arg Gln Arg Ser Leu Gly Pro Asp
            740                 745                 750

Ala Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr
        755                 760                 765

Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile
    770                 775                 780

Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln
785                 790                 795                 800

Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr
                805                 810                 815

Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro
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Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser
    850                 855                 860

Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe
865                 870                 875                 880

Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp
                885                 890                 895

Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe
            900                 905                 910

Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg
        915                 920                 925

Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp
    930                 935                 940

Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys
945                 950                 955                 960

Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr
                965                 970                 975

Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu
            980                 985                 990

Val Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Lys
        995                1000                1005

Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly
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Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu
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Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr
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Pro Met Ser His Pro Lys Ser Ser Ser Thr Gly Val Gly Glu Ala Leu
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Gly Ser Gly Ser Arg Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly
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His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser
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Arg Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser
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Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp
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Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp
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His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp
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Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly
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Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser
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Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly
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Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln
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Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser
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Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys
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His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile
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Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp
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Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe
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Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly
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Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg
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Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly
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Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly
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Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
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Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp
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Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg
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Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
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Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr
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Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His
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Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala
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Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
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Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu
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Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Ser Lys Glu Lys Gln
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Met Ala Glu Ala Gln Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe
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Ala Ile Val Leu Leu Ser Ile Met Gly Ile Thr Leu Glu Glu Ile Glu
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Val Asn Leu Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg
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Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly
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Met Arg Ala Leu Leu His Thr Val Met Gln Ala Leu Pro Gln Val Gly
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Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu
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Gly Val Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys
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Glu Gly Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe
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Leu Thr Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met
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Lys Asp Pro Ser Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr
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Val Ile Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe
1825 1830 1835 1840

Val Leu Val Asn Val Val Ile Ala Val Leu Met Lys His Leu Glu Glu
1845 1850 1855

Ser Asn Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu
1860 1865 1870

Leu Glu Met Lys Thr Leu Ser Pro Gln Pro His Ser Pro Leu Gly Ser
1875 1880 1885

Pro Phe Leu Trp Pro Gly Val Glu Gly Val Asn Ser Thr Asp Ser Pro
1890 1895 1900

Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala Ser Gly
1905 1910 1915 1920

Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu Val Pro
1925 1930 1935

Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser
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Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys Arg Asn Gly Ser
1955 1960 1965

Thr Ala Glu Arg Ser Leu Gly His Arg Gly Trp Gly Leu Pro Lys Ala
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Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser
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Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln Pro His
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Gly Ala Pro Thr Trp Gly Ala Ile Pro Lys Leu Pro Pro Pro Gly Arg
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Asp Glu Glu Gln Pro Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
65                  70                  75                  80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
                85                  90                  95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
            100                 105                 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
        115                 120                 125

Arg Ser Glu Arg Cys Ser Ile Leu Glu Ala Phe Asp Asp Phe Ile Phe
    130                 135                 140

Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
145                 150                 155                 160

Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe
                165                 170                 175

Phe Ile Val Met Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Lys
            180                 185                 190

Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
        195                 200                 205

Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
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Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225                 230                 235                 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
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Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
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Phe Ile Cys Ser Ser Arg Arg Asp Asn Gly Met Gln Lys Cys Ser His
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Ile Pro Ser Arg Arg Glu Leu Arg Val Gln Cys Thr Leu Gly Trp Glu
305                 310                 315                 320

Ala Tyr Gly Gln Pro Gln Ala Glu Asp Gly Gly Ala Gly Arg Asn Ala
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Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Glu Phe
            340                 345                 350

Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
        355                 360                 365

Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
    370                 375                 380

Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
385                 390                 395                 400

Leu Leu Ile Ile Met Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val
                405                 410                 415

Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Asn Gln Leu
            420                 425                 430

Met Arg Glu Gln Arg Ala Arg Tyr Leu Ser Asn Asp Ser Thr Leu Ala
        435                 440                 445

Ser Phe Ser Glu Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Val
    450                 455                 460

Gly His Ile Phe Arg Lys Val Lys Arg Arg Ser Leu Arg Leu Tyr Ala
465                 470                 475                 480

Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ser Thr Val
                485                 490                 495

His Gly Gln Gly Pro Gly Arg Arg Pro Arg Arg Ala Gly Arg Arg Thr
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Ala Ser Val His His Leu Val Tyr His His His His His His His His
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His Tyr His Phe Ser His Gly Gly Pro Arg Arg Pro Ser Pro Glu Pro
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Gly Ala Gly Asp Asn Arg Leu Val Arg Ala Cys Ala Pro Pro Ser Pro
545                 550                 555                 560

Pro Ser Pro Gly His Gly Pro Pro Asp Ser Glu Ser Val His Ser Ile
                565                 570                 575

Tyr His Ala Asp Cys His Val Glu Gly Pro Gln Glu Arg Ala Arg Val
            580                 585                 590

Ala His Ser Ile Ala Thr Ala Ala Ser Leu Lys Leu Ala Ser Gly Leu
        595                 600                 605

Gly Thr Met Asn Tyr Pro Thr Ile Leu Pro Ser Gly Thr Val Asn Ser
    610                 615                 620

Lys Gly Gly Thr Ser Ser Arg Pro Lys Gly Leu Arg Gly Ala Gly Ala
625                 630                 635                 640

Pro Gly Ala Ala Val His Ser Pro Leu Ser Leu Gly Ser Pro Arg Pro
                645                 650                 655

Tyr Glu Lys Ile Gln Asp Val Val Gly Glu Gln Gly Leu Gly Arg Ala
            660                 665                 670

Ser Ser His Leu Ser Gly Leu Ser Val Pro Cys Pro Leu Pro Ser Pro
        675                 680                 685

Gln Ala Gly Thr Leu Thr Cys Glu Leu Lys Ser Cys Pro Tyr Cys Ala
    690                 695                 700

Ser Ala Leu Glu Asp Pro Glu Phe Glu Phe Ser Gly Ser Glu Ser Gly
705                 710                 715                 720

Asp Ser Asp Ala His Gly Val Tyr Glu Phe Thr Gln Asp Val Arg His
                725                 730                 735

Gly Asp Cys Arg Asp Pro Val Gln Gln Pro His Glu Val Gly Thr Pro
            740                 745                 750

Gly His Ser Asn Glu Arg Arg Arg Thr Pro Leu Arg Lys Ala Ser Gln
        755                 760                 765

Pro Gly Gly Ile Gly His Leu Trp Ala Ser Phe Ser Gly Lys Leu Arg
    770                 775                 780
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Arg Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Ala Ala Ile
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Leu Val Asn Thr Leu Ser Met Gly Val Glu Tyr His Glu Gln Pro Glu
                805                 810                 815

Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr Ser Met
            820                 825                 830

Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Ala Cys Gly Pro Leu Gly
        835                 840                 845

Tyr Ile Arg Asn Pro Tyr Asn Ile Phe Asp Gly Ile Val Val Val Ile
    850                 855                 860

Ser Val Trp Glu Ile Val Gly Gln Ala Asp Gly Gly Gln Ser Val Leu
865                 870                 875                 880

Arg Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe Leu Pro
                885                 890                 895

Ala Leu Arg Arg Gln Leu Val Val Leu Met Arg Thr Met Asp Asn Val
            900                 905                 910

Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser Ile
        915                 920                 925

Leu Gly Met His Leu Phe Gly Cys Lys Phe Ser Leu Lys Thr Asp Ser
    930                 935                 940

Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala
945                 950                 955                 960

Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Val Val
                965                 970                 975

Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr Phe
            980                 985                 990

Val Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu Val
        995                1000                1005

Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Arg Ser
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Asp Thr Asp Glu Asp Lys Thr Ser Thr Gln Leu Glu Gly Asp Phe Asp
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Lys Leu Arg Asp Leu Arg Ala Thr Glu Met Lys Met Tyr Ser Leu Ala
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Val Thr Pro Asn Gly His Leu Glu Gly Arg Gly Ser Leu Pro Pro Pro
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Leu Ile Thr His Thr Ala Ala Thr Pro Met Pro Thr Pro Lys Ser Ser
        1075                1080                1085

Pro Asn Leu Asp Val Ala His Ala Leu Leu Asp Ser Arg Arg Ser Ser
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Ser Gly Ser Val Asp Pro Gln Leu Gly Asp Gln Lys Ser Leu Ala Ser
1105                1110                1115                1120

Leu Arg Ser Ser Pro Cys Thr Pro Trp Gly Pro Asn Ser Ala Gly Ser
                1125                1130                1135

Ser Arg Arg Ser Ser Trp Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys
            1140                1145                1150

Arg Arg Ser Gln Cys Gly Glu Arg Glu Ser Leu Leu Ser Gly Glu Gly
        1155                1160                1165

Lys Gly Ser Thr Asp Asp Glu Ala Glu Asp Ser Arg Pro Ser Thr Gly
    1170                1175                1180

Thr His Pro Gly Ala Ser Pro Gly Pro Arg Ala Thr Pro Leu Arg Arg
1185                1190                1195                1200

Ala Glu Ser Leu Asp His Arg Ser Thr Leu Asp Leu Cys Pro Pro Arg
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Pro Ala Pro Pro Ala Val Gln Val His Asp Cys Asn Gly Gln Met Val
            1220                1225                1230

Ala Leu Pro Ser Glu Phe Phe Leu Arg Ile Asp Ser His Lys Glu Asp
        1235                1240                1245

Ala Ala Glu Phe Asp Asp Asp Ile Glu Asp Ser Cys Cys Phe Arg Leu
    1250                1255                1260

His Lys Val Leu Glu Pro Tyr Ala Pro Gln Trp Cys Arg Ser Arg Glu
1265                1270                1275                1280

Ser Trp Ala Leu Tyr Leu Phe Pro Pro Gln Asn Arg Leu Arg Val Ser
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Cys Gln Lys Val Ile Ala His Lys Met Phe Asp His Val Val Leu Val
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Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Asp Ile
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Asp Pro Gly Ser Thr Glu Arg Ala Phe Leu Ser Val Ser Asn Tyr Ile
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Phe Thr Ala Ile Phe Val Val Glu Met Met Val Lys Val Val Ala Leu
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Gly Leu Leu Trp Gly Glu His Ala Tyr Leu Gln Ser Ser Trp Asn Val
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Leu Asp Gly Leu Leu Val Leu Val Ser Leu Val Asp Ile Ile Val Ala
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Met Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Val
       1395                1400                1405

Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro
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Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Arg Pro Ile
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Gly Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile
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Leu Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr Tyr Cys Glu Gly Thr
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Asp Thr Arg Asn Ile Thr Thr Lys Ala Glu Cys His Ala Ala His Tyr
       1475                1480                1485

Arg Trp Val Arg Arg Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu
   1490                1495                1500

Met Ser Leu Phe Val Leu Ser Ser Lys Asp Gly Trp Val Asn Ile Met
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Tyr Asp Gly Leu Asp Ala Val Gly Ile Asp Gln Gln Pro Val Gln Asn
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His Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val
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Glu Lys Arg Leu Arg Arg Leu Glu Arg Arg Arg Arg Lys Ala Gln Arg
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Arg Pro Tyr Tyr Ala Asp Tyr Ser His Thr Arg Arg Ser Ile His Ser
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Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr Phe Ile Ile Cys
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Phe Lys Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser
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Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg
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Val Leu Lys Leu Leu Lys Met Ala Thr Gly Met Arg Ala Leu Leu Asp
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Thr Val Val Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe
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Met Leu Leu Phe Phe Ile Tyr Ala Ala Leu Gly Val Glu Leu Phe Gly
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Arg Leu Glu Cys Ser Glu Asp Asn Pro Cys Glu Gly Leu Ser Arg His
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Ala Thr Phe Thr Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val
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Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Glu
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Cys Thr Arg Glu Asp Lys His Cys Leu Ser Tyr Leu Pro Ala Leu Ser
1825 1830 1835 1840

Pro Val Tyr Phe Val Thr Phe Met Leu Val Ala Gln Phe Val Leu Val
1845 1850 1855

Asn Val Val Val Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys
1860 1865 1870

Glu Ala Arg Glu Asp Ala Glu Met Asp Ala Glu Ile Glu Leu Glu Met
1875 1880 1885

Ala Gln Gly Ser Thr Ala Gln Pro Pro Pro Thr Ala Gln Glu Ser Gln
1890 1895 1900

Gly Thr Gln Pro Asp Thr Pro Asn Leu Leu Val Val Arg Lys Val Ser
1905 1910 1915 1920

Val Ser Arg Met Leu Ser Leu Pro Asn Asp Ser Tyr Met Phe Arg Pro
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Val Ala Pro Ala Ala Ala Pro His Ser His Pro Leu Gln Glu Val Glu
1940 1945 1950

Met Glu Thr Tyr Thr Gly Pro Val Thr Ser Ala His Ser Pro Pro Leu
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Glu Pro Arg Ala Ser Phe Gln Val Pro Ser Ala Ala Ser Ser Pro Ala
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Arg Val Ser Asp Pro Leu Cys Ala Leu Ser Pro Arg Gly Thr Pro Arg
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Ser Leu Ser Leu Ser Arg Ile Leu Cys Arg Gln Glu Ala Met His Ser
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Glu Ser Leu Glu Gly Lys Val Asp Asp Val Gly Gly Asp Ser Ile Pro
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Asp Tyr Thr Glu Pro Ala Glu Asn Met Ser Thr Ser Gln Ala Ser Thr
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Thr Arg Lys His Thr Phe Gly Gln Arg Cys Ile Ser Ser Arg Pro Pro
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His Pro Asp Leu Ala Pro Val Ala Phe Phe Cys Leu Arg Gln Thr Thr
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Ser Pro Arg Asn Trp Cys Ile Lys Met Val Cys Asn Pro Trp Phe Glu
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Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly Met
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Tyr Gln Pro Cys Asp Asp Met Glu Cys Leu Ser Asp Arg Cys Lys Ile
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Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
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Cys Pro His Cys Gln His Glu Ala Gly Arg Arg Pro Ser Gly Leu Gly
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Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
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Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val
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Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
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Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
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Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
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Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
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Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
            340                 345                 350

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
        355                 360                 365

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
    370                 375                 380

Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
385                 390                 395                 400

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
                405                 410                 415

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
            420                 425                 430

Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
        435                 440                 445

Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu
    450                 455                 460

Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser
465                 470                 475                 480

Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
                485                 490                 495

His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
            500                 505                 510

Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly
        515                 520                 525
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Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly
    530                 535                 540

Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp
545                 550                 555                 560

Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro
                565                 570                 575

Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr
            580                 585                 590

Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val
        595                 600                 605

Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile
    610                 615                 620

Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser
625                 630                 635                 640

Thr Gly Ala Cys
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<210> 32
<211> 1608
<212> DNA
<213> HUMAN

<400> 32
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cggcgttggt gggggcgtcc ccggagagcc ccggggcgcc gggacgcgag gcggagcggg 180
ggtccgagct cggcgtgtca ccctccgaga gcccggcggc cgagcgcggc gcggagctgg 240
gtgccgacga ggagcagcgc gtcccgtacc cggccttggc ggccacggtc ttcttctgcc 300
tcggtcagac cacgcggccg cgcagctggt gcctccggct ggtctgcaac ccatggttcg 360
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gtgaggacgt tgagtgcggc tccgagcgct gcaacatcct ggaggccttt gacgccttca 480
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agaagtgtta cctgggtgac acgtggaaca ggctggattt cttcatcgtc gtggcgggca 600
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agggcgagga gaacccgttc atctgctcct cacgccgaga caacggcatg cagaagtgct 960
cgcacatccc cggccgccgc gagctgcgca tgccctgcac cctgggctgg gaggcctaca 1020

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cgcagccgca ggccgagggg gtgggcgctg cacgcaacgc ctgcatcaac tggaaccagt 1080
actacaacgt gtgccgctcg ggtgactcca acccccacaa cggtgccatc aacttcgaca 1140
acatcggcta cgcctggatc gccatcttcc aggtgatcac gctggaaggc tgggtggaca 1200
tcatgtacta cgtcatggac gcccactcat tctacaactt catctatttc atcctgctca 1260
tcatcgtggg ctccttcttc atgatcaacc tgtgcctggt ggtgattgcc acgcagttct 1320
cggagacgaa gcagcgggag agtcagctga tgcgggagca gcgggcacgc cacctgtcca 1380
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agagccgctg gcgcaagaag gtggacccca gtgctgtgca aggccagggt cccgggcacc 1560
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<210> 33
<211> 518
<212> PRT
<213> HUMAN

<400> 33
Met Thr Glu Gly Ala Arg Ala Ala Asp Glu Val Arg Val Pro Leu Gly
  1               5                  10                  15

Ala Pro Pro Pro Gly Pro Ala Ala Leu Val Gly Ala Ser Pro Glu Ser
             20                  25                  30

Pro Gly Ala Pro Gly Arg Glu Ala Glu Arg Gly Ser Glu Leu Gly Val
         35                  40                  45

Ser Pro Ser Glu Ser Pro Ala Ala Glu Arg Gly Ala Glu Leu Gly Ala
     50                  55                  60

Asp Glu Glu Gln Arg Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
 65                  70                  75                  80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
                 85                  90                  95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
            100                 105                 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
        115                 120                 125

Gly Ser Glu Arg Cys Asn Ile Leu Glu Ala Phe Asp Ala Phe Ile Phe
    130                 135                 140

Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
145                 150                 155                 160

Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe
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165 170 175

Phe Ile Val Val Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Asn
180 185 190

Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
195 200 205

Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
210 215 220

Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225 230 235 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
245 250 255

Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
260 265 270

Thr Phe Leu Arg Pro Tyr Tyr Gln Thr Glu Glu Gly Glu Glu Asn Pro
275 280 285

Phe Ile Cys Ser Ser Arg Arg Asp Asn Gly Met Gln Lys Cys Ser His
290 295 300

Ile Pro Gly Arg Arg Glu Leu Arg Met Pro Cys Thr Leu Gly Trp Glu
305 310 315 320

Ala Tyr Thr Gln Pro Gln Ala Glu Gly Val Gly Ala Ala Arg Asn Ala
325 330 335

Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Asp Ser
340 345 350

Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
355 360 365

Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
370 375 380

Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
385 390 395 400

Leu Leu Ile Ile Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val
405 410 415

Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu

420 425 430

Met Arg Glu Gln Arg Ala Arg His Leu Ser Asn Asp Ser Thr Leu Ala
435 440 445

Ser Phe Ser Glu Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Val
450 455 460

Gly His Ile Phe Arg Lys Val Lys Arg Arg Ser Leu Arg Leu Tyr Ala
465 470 475 480

Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ala Val Gln
485 490 495

Gly Gln Gly Pro Gly His Arg Gln Arg Arg Ala Gly Arg His Thr Ala
500 505 510

Ser Val His His Leu Val
515

<210> 34
<211> 1080
<212> DNA
<213> HUMAN

<400> 34
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acagcctcaa gcacaagccg ccgtcggcgg agcatgagtc cctgctctct gcggagcgcg 180
gcggcggcgc ccgggtctgc gaggttgccg cggacgaggg gccgccgcgg gccgcacccc 240
tgcacacccc acacgcccac cacattcatc acgggcccca tctggcgcac cgccaccgcc 300
accaccgccg gacgctgtcc ctcgacaaca gggactcggt ggacctggcc gagctggtgc 360
ccgcggtggg cgcccacccc cgggccgcct ggagggcggc aggcccggcc cccgggcatg 420
aggactgcaa tggcaggatg cccagcatcg ccaaagacgt cttcaccaag atgggcgacc 480
gcggggatcg cggggaggat gaggaggaaa tcgactacac cctgtgcttc cgcgtccgca 540
agatgatcga cgtctataag cccgactggt gcgaggtccg cgaagactgg tctgtctacc 600
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tcgactacgt cgtcctggcc ttcatctttc tcaactgcat caccatcgcc ctggagcggc 720
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cggccatctt cgtgggcgag atgacattga aggtagtctc gctgggcctg tacttcggcg 840
agcaggcgta cctacgcagc agctggaacg tgctggatgg ctttcttgtc ttcgtgtcca 900
tcatcgacat cgtggtgtcc ctggcctcag ccgggggagc caagatcttg ggggtcctcc 960
gagtcttgcg gctcctgcgc accctacgcc ccctgcgtgt catcagccgg gcgccgggcc 1020
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<210> 35
<211> 359

<212> PRT
<213> HUMAN

<400> 35

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Ser Val Met Ser Leu Gly Arg Met Ser Tyr Asp Gln Arg Ser Leu Ser
  1               5                  10                  15

Ser Ser Arg Ser Ser Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp
             20                  25                  30

Ala Ser Arg Arg Ser Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser
         35                  40                  45

Ala Glu His Glu Ser Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg
     50                  55                  60

Val Cys Glu Val Ala Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu
 65                  70                  75                  80

His Thr Pro His Ala His His Ile His His Gly Pro His Leu Ala His
                 85                  90                  95

Arg His Arg His His Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser
            100                 105                 110

Val Asp Leu Ala Glu Leu Val Pro Ala Val Gly Ala His Pro Arg Ala
        115                 120                 125

Ala Trp Arg Ala Ala Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly
    130                 135                 140

Arg Met Pro Ser Ile Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg
145                 150                 155                 160

Gly Asp Arg Gly Glu Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe
                165                 170                 175

Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro Asp Trp Cys Glu Val
            180                 185                 190

Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro Glu Asn Arg Phe Arg
        195                 200                 205

Val Leu Cys Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val
    210                 215                 220

Leu Ala Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro
225                 230                 235                 240
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Gln Ile Glu Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn
                245                 250                 255

Tyr Ile Phe Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val
            260                 265                 270

Ser Leu Gly Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp
        275                 280                 285

Asn Val Leu Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val
    290                 295                 300

Val Ser Leu Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg
305                 310                 315                 320

Val Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg
                325                 330                 335

Ala Pro Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys
            340                 345                 350

Pro Ile Gly Asn Ile Val Leu
        355
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